

**DISCREPANCIES BETWEEN PATIENT AND CAREGIVER  
APATHY RATINGS IN MILD ALZHEIMER'S DISEASE**

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*Wie geht es dir, Papa?*

*Also, ich muss sagen, es geht mir gut. Allerdings unter Anführungszeichen, denn ich bin  
nicht imstande, es zu beurteilen.*

(Arno Geiger, Der alte König in seinem Exil)



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## ABSTRACT

Considerable differences between self-reports by individuals with dementia and informant reports by their caregivers are well documented and consistent across domains and patient populations. Investigations revealed that patients' ratings regarding their suffering are consistently lower than the ratings of their caregivers.

The aim of the present cumulative PhD thesis was to provide a contribution to the current understanding of the discrepancy of rating apathy in mild Alzheimer's disease through the examination of three aspects: the multifactoriality, the domain specificity, and the temporal course of rating discrepancy. The findings are based on three research articles (Papers 1, 2, and 3).

The main purpose of Paper 1, a cross-sectional study, was to investigate domain-specific relationships between caregiver burden or depression and rating discrepancies of depression, apathy, activities of daily living, and quality of life. Papers 2 and 3 examined longitudinally the rating discrepancy in apathy with a particular focus on the distinction between the positive and negative rating discrepancies (Paper 2) and in relation to a multicomponent cognitive-behavioural treatment and a treatment as usual (Paper 3).

The findings of all three papers indicate the presence of caregiver rating bias in rating discrepancies in mild Alzheimer's disease. The data of Paper 1 revealed that caregiver burden might be a more important predictor of caregiver rating bias than caregiver depression. Paper 2 contributed to the evidence that positive and negative rating discrepancies reflect distinct underlying processes, since a negative rating discrepancy predicted clinical apathy at follow-up. These findings suggest a multifactoriality of rating discrepancy. Furthermore, the findings of Papers 1 and 3 support the assumption of domain specificity in rating discrepancies with regard to the magnitude, the predictor structure, and the longitudinal course. The longitudinal

studies (Papers 2 and 3) showed inconsistent findings regarding the temporal course of the rating discrepancy of apathy. In Paper 2, rating discrepancy increased and in Paper 3, it remained constant in the CBT group and it decreased in the TAU group within one year. This indicates that patient and caregiver ratings should be considered separately in exploring the longitudinal course of rating discrepancies.

The findings of the three papers have been integrated to draw general conclusions and to give implications for research and clinical practice. From these, the following information can be derived about rating discrepancy in apathy in that it functions as an indicator of caregiver burden and the potential of caregiver rating bias, as a measure of awareness of deficits, as a reflection of dyadic processes, as a risk factor for a clinical apathy, and as an indicator of differential effects of psychosocial interventions.

In conclusion, the present thesis provides an impulse for a change of perspective in relation to the background and interpretation of rating discrepancies. It suggests the need for further research, especially regarding the capability of rating discrepancy as a useful, economical source of information in clinical practice.



## ZUSAMMENFASSUNG

Unterschiede zwischen der Selbsteinschätzung von dementiell erkrankten Patienten und der Fremdeinschätzung durch deren Betreuungspersonen sind in der Literatur gut dokumentiert und zeigen sich konsistent über verschiedenen Symptombereiche und über unterschiedliche Patientengruppen hinweg. Mehrheitlich überschätzt der Angehörige die Beeinträchtigung oder das Leiden im Vergleich zur Selbsteinschätzung des Patienten.

Die vorliegende kumulative Dissertation hat zum Ziel drei Aspekte der oben genannten Urteilerdiskrepanzen zu untersuchen: Die Multifaktorialität, die Domänenspezifität und den zeitlichen Verlauf. Damit soll ein Beitrag zum besseren Verständnis von Urteilerdiskrepanzen von Apathie bei Demenz vom Alzheimer Typ im Frühstadium geleistet werden. Die Forschungsergebnisse dieser Dissertation basieren auf drei wissenschaftlichen Artikeln (Artikel 1, 2 und 3).

Artikel 1, eine Querschnittstudie, beabsichtigte die Beziehung zwischen der Angehörigenbelastung bzw. der Depression von Angehörigen und der Urteilerdiskrepanz von Depression, Apathie, Aktivitäten des täglichen Lebens und Lebensqualität zu untersuchen. Artikel 2 und 3 hatten das Ziel, Urteilerdiskrepanzen von Apathie im Längsschnitt zu evaluieren. Dies einerseits mit einem Fokus auf die Differenzierung von positiven und negativen Diskrepanzen (Artikel 2) und andererseits im Zusammenhang mit einer psychosozialen multimodularen Intervention und einer üblichen Behandlung (Artikel 3).

Die Ergebnisse aller drei Artikel weisen auf eine generelle Überschätzung des Angehörigen der Symptome des Patienten hin (caregiver rating bias). Die Resultate von Artikel 2 zeigen zudem auf, dass positive und negative, beziehungsweise unterschätzende und überschätzende Urteilerdiskrepanzen, differenziert betrachtet werden sollten, da sich dahinter unterschiedliche Prozesse zu verbergen scheinen. In Artikel 2 sagten negative

Urteilerdiskrepanzen von Apathie eine klinische Diagnose einer Apathie ungefähr ein Jahr später voraus. Diese Befunde sprechen für die Multifaktorialität von Urteilerdiskrepanzen, d.h. der Urteilerdiskrepanz liegen unterschiedliche Prozess zugrunde.

Des Weiteren konnten die Befunde von Artikel 1 und 3 die Annahme einer Domänenspezifität bei Urteilerdiskrepanzen in Bezug auf die Ausprägung, Prädiktoren und den zeitlichen Verlauf bestätigen. Die Längsschnittstudien (Artikel 2 und 3) zeigten unterschiedliche Entwicklungen der Urteilerdiskrepanzen von Apathie über die Zeit. Ohne Behandlung nahm die Urteilerdiskrepanz zu (Artikel 2), während sie in der Interventionsgruppe konstant blieb und sich in der Gruppe mit der üblichen Behandlung verringerte (Artikel 3). Diese Ergebnisse legen nahe, bei längsschnittlichen Untersuchungen von Urteilerdiskrepanzen zusätzlich die Selbsteinschätzung der Patienten und die Fremdeinschätzung der Angehörigen separat zu betrachten.

Die Befunde der drei Artikel werden in der Diskussion miteinander verglichen, allgemeine Schlussfolgerungen werden gezogen und Implikationen für die Forschung und die klinische Praxis werden aufgezeigt. Man kann aus den Ergebnissen der Studien dieser Dissertation Hinweise für unterschiedliche Funktionen der Urteilerdiskrepanz bei Apathie herleiten; als ein Indikator für Angehörigenbelastung und das mögliche Vorliegen von einer Verzerrung des Angehörigen Ratings, als Messinstrument für Krankheitseinsicht, als ein Spiegel dyadischer Prozesse, als Risikofaktor für klinisch bedeutsame Apathie und als Indikator für differentielle Effekte psychosozialer Interventionen.

Die vorliegende Arbeit soll einen Impuls für eine neue Sicht auf die Hintergründe und Interpretationsmöglichkeiten von Urteilerdiskrepanzen geben. In dieser Arbeit wird dafür plädiert, Urteilerdiskrepanzen weiter zu untersuchen und deren Potential als hilfreiche, ökonomische Informationsquellen in der klinischen Praxis zu erkunden.

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# 1 INTRODUCTION

In dementia research and clinical practice it is common to integrate information from different sources, e.g. patients' self-reports and informer reports by a caregiver to gain insight into the well-being of the patients (Perkins, 2007; Stella et al., 2015). Reliability of patients' self-ratings of neuropsychiatric symptoms in mild cognitive impairment (MCI) and mild Alzheimer's disease (AD) has been demonstrated (Arlt et al., 2008; Bradford et al., 2013; Perkins, 2007). Likewise, caregivers seem to be a very accurate and a valuable source at diagnosing neuropsychiatric symptoms and everyday functioning in cognitively impaired individuals, given their intimacy with the patient's situation and experiences in everyday life (Dujardin, Sockeel, Delliaux, Destée, & Defebvre, 2008; Perkins, 2007; Rueda et al., 2014).

However, significant differences between self-reports by individuals with dementia and informant reports by their caregivers are well documented and consistent across domains and patient populations (Chopra, Sullivan, Feldman, Landes, & Beck, 2008; Clare, Nelis, Martyr, Roberts, et al., 2012; Leicht, Berwig, & Gertz, 2010; Rueda et al., 2014; Sands, Ferreira, Stewart, Brod, & Yaffe, 2004; Snow, Cook, Lin, Morgan, & Magaziner, 2005). These investigations reveal that patients' ratings regarding their suffering are consistently lower than the ratings of their caregivers.

Most of the studies concerning patient-caregiver rating discrepancies in AD focus on the domains memory, quality of life (QoL), and activities of daily living (ADL) (Bertrand & Willis, 1999; Bosboom, Alfonso, Eaton, & Almeida, 2012; Clare, Nelis, Martyr, Roberts, et al., 2012; Rueda et al., 2014; Sands et al., 2004), but studies that investigate apathy rating discrepancy are relatively underrepresented in literature.

Certain aspects, however, of the rating discrepancy in apathy, or rather, the factors that influence perceived apathy in patients and caregivers, require further clarification. The aim,

therefore, of this thesis was to elucidate some answers about the multifactoriality (i.e. the components and direction of rating discrepancy), the domain specificity, and the temporal development of rating discrepancy in apathy.

This cumulative thesis consisting of three research papers (labelled Papers 1, 2, and 3) is structured as follows. The *Theoretical Background* section presents concepts, empirical findings, and the relevance of rating discrepancies in mild AD, with a special focus on rating discrepancies in apathy. The *Present Thesis* section summarizes the three research articles. The main purpose of Paper 1, a cross-sectional study, was to examine domain-specific relationships between caregiver burden or depression and rating discrepancies in depression, apathy, ADL, and QoL. Papers 2 and 3 examined longitudinally rating discrepancy in apathy as well as patients' and caregivers' apathy ratings. In Paper 2, a particular focus was set on the distinction between the positive and negative rating discrepancies and its predictive value for a clinical diagnosis of apathy. In Paper 3, rating discrepancy in apathy was examined in relation to a multicomponent cognitive-behavioural treatment (CBT) and a treatment as usual.

The findings of the three papers are then brought together in the *General Discussion* section in which the aspects of multifactoriality, domain specificity, and the temporal development of rating discrepancies in apathy are considered. In addition, implications for research and clinical practice are derived, followed by the final conclusions. The manuscripts of the three papers are provided in full length at the end of this work.

## 2 THEORETICAL BACKGROUND

### 2.1 Alzheimer's Disease and Neuropsychiatric Symptoms

AD is the most common progressive neurodegenerative disorder in cognitively impaired elderly patients and accounts for an estimated 60% to 80% of cases (Alzheimer's Association, 2014). The clinical diagnosis of AD in the papers corresponded to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 2000). It also required a gradual onset and progressive deterioration of cognitive functioning and the exclusion of all other specific causes of dementia. The deterioration of cognitive functioning, manifested in terms of memory impairments (in the ability to learn or recall information) and at least one cognitive disturbance, including aphasia (language disturbance), apraxia (impaired motor activity), agnosia (recognition/ identification failure of nine objects), and executive function disturbance (e.g. planning, and judgement).

Neuropsychiatric symptoms are remarkably prevalent in AD and affect approximately 42% of the patients with mild, 80% with moderate, and over 90% with severe AD (Apostolova et al., 2014). In mild AD the most frequent neuropsychiatric symptoms are irritability, apathy, depression, anxiety, and agitation (Vogel, Waldorff, & Waldemar, 2010) and as the disease progresses, delusions, hallucinations, and aggression become more frequent as well (Lyketsos et al., 2011). Neuropsychiatric symptoms are associated with major adverse effects on daily function, cognitive decline, QoL, earlier institutionalization, and caregiver burden (Apostolova et al., 2014; Lyketsos et al., 2011; Ornstein & Gaugler, 2012; Steinberg et al., 2006). Risk factors for neuropsychiatric symptoms in mild AD are younger age, male gender, and greater functional impairment (Apostolova et al., 2014).

## 2.2 Apathy in Alzheimer's Disease

The term apathy is derived from the Greek original *apatheia* (derived from *apathēs* meaning 'without feeling', from *a* meaning 'not' and *pathos* meaning 'suffering') (Robert et al., 2009). Marin (1990, 1991) originally defined apathy as a lack of motivation, manifest in diminished goal-directed behaviour, cognition, and emotional concomitants. Subsequently, Starkstein and colleagues (2001) have developed a set of diagnostic criteria for apathy, which specify the following as core features: diminished motivation, initiative and interest, and blunting of emotions. To reach consensus on diagnostic criteria, an international task force set them according to the proposal by Robert and colleagues (2009) (see Table 1). There is no consensus as to whether apathy should be considered as a neuropsychiatric symptom, or as a syndrome on its own (Starkstein & Leentjens, 2008). Definitions of apathy and depression overlap in terms of key symptoms, but apathy is considered to be a loss of motivation without clinical dysphoric symptoms such as sadness, feelings of guilt, self-criticism, helplessness, and hopelessness (Cummings et al., 2015; Mortby, Maercker, & Forstmeier, 2012).

Table 1 Proposed diagnostic criteria for apathy based on International Task Force Consensus Criteria (Robert et al., 2009)

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For a diagnosis of Apathy the patient should fulfil the criteria A, B, C and D.

A. Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.

B. Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time

Domain B1: Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following:

- Loss of self-initiated behaviour (for example, starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)
- Loss of environment-stimulated behaviour (for example, responding to conversation, participating in social activities)

Domain B2: Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:

- Loss of spontaneous ideas and curiosity for routine and new events (for example, challenging tasks, recent news, social opportunities, personal/family and social affairs)
- Loss of environment-stimulated ideas and curiosity for routine and new events (for example, in the person's residence, neighbourhood or community)

Domain B3: Loss of, or diminished, emotion as evidenced by at least one of the following:

- Loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect)
- Loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news)

C. These symptoms (A-B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.

D. The symptoms (A-B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication).

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Apathy is the most persistent and frequent neuropsychiatric symptom throughout all stages of AD and increases in the course of the cognitive decline (Brodaty, Connors, Xu, Woodward, & Ames, 2015; Di Iulio et al., 2010; Landes, Sperry, & Strauss, 2005; Lyketsos et al., 2011; Onyike et al., 2007). The reported prevalence of apathy in mild AD ranged from 25.2% (Onyike et al., 2007) to 42.2% (Landes et al., 2005). Apathy is associated with male

gender (Apostolova et al., 2014) and many adverse outcomes, such as conversion from MCI to AD (Robert et al., 2006), cognitive decline (Lechowski et al., 2009; Starkstein, Jorge, Mizrahi, & Robinson, 2006b), functional decline (Apostolova et al., 2014; Clarke, Ko, Lyketsos, Rebok, & Eaton, 2010; Lechowski et al., 2009; Starkstein et al., 2006b), executive dysfunctions (Drijgers, Verhey, Leentjens, Köhler, & Aalten, 2011), depression (Starkstein et al., 2006b), unawareness of cognitive symptoms (Mograbie & Morris, 2014; Starkstein, Brockman, Bruce, & Petracca, 2010), lower QoL (Groeneweg-Koolhoven, de Waal, van der Weele, Gussekloo, & van der Mast, 2014), and lower self-efficacy beliefs (Esposito, Gendolla, & Van der Linden, 2014). Apathy is also related to caregiver burden and fewer positive experiences in caregiving (Brodaty & Burns, 2012; de Vugt et al., 2003; Landes, Sperry, Strauss, & Geldmacher, 2001; Onyike et al., 2007).

### **2.2.1 Nonpharmacological Treatment of Apathy in Dementia**

A wide range of approaches have been developed to treat neuropsychiatric symptoms of dementia (Brodaty & Burns, 2012; Politis et al., 2004; Treusch et al., 2011). A review of 56 studies demonstrated that individuals with apathy benefit most from therapeutic activity intervention, including stimulation, creative activities, cooking, Montessori methods, and behavioural elements (Brodaty & Burns, 2012). Likewise, reminiscence group therapy seems to be effective in the treatment of apathy in patients with mild to moderate dementia (Hsieh et al., 2010). In general, helpful interventions were often tailored individually, including personal history, previous interests, and environmental factors (Brodaty & Burns, 2012; Jao, Algate, Specht, & Williams, 2015; Treusch et al., 2011). Moreover, if present, general medical conditions should be treated and sensory deficits should be corrected. Finally, environmental modifications may also be beneficial to enhance motivation (Ishii, Weintraub, & Mervis, 2009).

## 2.3 Multifactoriality of Rating Discrepancy

Table 2 gives an overview of different studies that investigated individual predictors of rating discrepancies of different domains. It has not the claim to be exhaustive, but it gives indication that rating discrepancy is a multifactorial construct consisting of characteristics of the patient, the caregiver, and the dyad. The variation of the reported factors that contribute to the rating discrepancies could be due to the divergences of the sample, the measurements, the variables, and the domains of the studies.

Table 2 Overview of studies investigating individual predictors of rating discrepancies (only predictors that have been found significant in the particular study are listed)

| Authors                                    | Domain             | Sample   | Predictors                                       |           |              |
|--|--------------------|--|--|-----------|--------------|
|  |                    |  | Patient  | Caregiver | Relationship |
| Bertrand & Willis, 1999                    | IADL               | <i>N</i> = 63, mild to moderate AD, mean MMSE score (SD) = 19.70 (3.97), primary caregiver: residing with the patient, 69% spouses | Age  |           |              |
| Bosboom et al., 2012                       | QoL-AD             | <i>N</i> = 80, mild to moderate AD, mean MMSE score (SD) = 14.70 (8.3), caregiver: regular contact with the patient, 61.4% spouses | Cognition, anxiety, NPS                          |           |              |
| Burke et al., 1998                         | Depression (GDS)   | <i>N</i> = 198, CDR = 1 or 2, mean MMSE score (SD) = 18.40 (5.4), caregiver: relatives   | Awareness, physical illness                      | Burden    |              |
| Chang et al., 2011                         | Depression (GDS)   | <i>N</i> = 155, CDR = 0.5-2, caregiver: 25.8% spouse, 50.7% adult child  |  | Burden    |              |
| Clare, Nelis, Martyr, Roberts et al., 2012 | Memory functioning | <i>N</i> = 101, MMSE > 18, mean MMSE score (SD) = 24.17 (2.81), caregiver: 66% spouse  | Age, depression, self-concept, conscientiousness | Stress    | Quality      |

Table 2 (continued)

|  |                              |   |   |                            |
|--|------------------------------|---|---|----------------------------|
| Clare, Nelis, Martyr, Roberts et al., 2012 | IADL                         | N = 101, MMSE > 18, mean MMSE score (SD) = 24.17 (2.81), caregiver: 66% spouse  | Age, anxiety, naming and letter fluency | Stress                     |
| Clare, Nelis, Whitaker, et al., 2012       | Marital Relationship Quality | N = 54, MMSE > 18, mean MMSE score (SD) = 24.37 (2.76), caregiver: spouse   | Depression                              | Stress                     |
| Fuh & Wang, 2006                           | QoL-AD                       | N = 90, mild to moderate AD, mean MMSE score (SD) = 20.10 (4.5), primary caregiver with everyday contact: 30% spouse, 57% adult child |   | Distress                   |
| Huang et al., 2009                         | QoL-AD                       | N = 120, CDR = 1-3, mean MMSE score (SD) = 18.64 (6.23), caregiver: > 50% spouse  |   | Quality                    |
| Martyr et al., 2014                        | IADL                         | N = 100, MMSE > 18, mean MMSE score (SD) = 24.17 (2.83), caregiver: 65% spouse  | Letter fluency                          |                            |
| Sands et al., 2004                         | DEM-QoL                      | N = 91, MMSE > 12, mean MMSE score (SD) = 19.70 (4.5), primary caregiver: > 50% spouse  | Depression                              | Burden                     |
| Schulz et al., 2013                        | QoL-AD                       | N = 79, mean MMSE score (SD) = 23.10 (3.6), primary caregiver: 73% spouse   |   | Physical and mental health |
| Tay et al., 2014                           | QoL-AD                       | N = 165, CDR 0.5-2, mean MMSE score (SD) = 18.40 (4.2), primary caregiver: 37% spouse, 56.4% adult child                              | Depression, NPS, education              |                            |

*Note.* IADL = Instrumental Activities of daily living; QoL-AD = Quality of life in AD; DEM-QoL = Quality of life in Dementia; GDS = Geriatric Depression Scale; NPS = Neuropsychiatric Symptoms; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating (0.5 = very mild, 1 = mild, 2 = moderate, 3 = severe dementia severity).



The calculation of discrepancy scores is a principal approach for assessing awareness of deficits in dementia (Clare, 2004). Therefore, a detailed overview of impaired awareness of deficits in dementia is given in the next section. Besides the level of awareness, rating discrepancy seems to be associated with the cognitive state (Bosboom et al., 2012; Clare, Nelis, Martyr, Roberts, et al., 2012; Martyr et al., 2011). Symptoms of AD could lead to inaccuracies in the ratings because the patients do not always remember all of the experiences they have had and language and reasoning deficits can impair patients' abilities to understand or respond to some of the items (Snow et al., 2005). In addition, patients' neuropsychiatric symptoms such as depression, anxiety, or apathy and demographics, such as age, gender, and education, are reported as predictors of rating discrepancies (Bertrand & Willis, 1999; Bosboom et al., 2012; Clare, Nelis, Martyr, Roberts, et al., 2012; Sands et al., 2004; Tay et al., 2014). Caregiver characteristics that bias caregiver ratings of patients' deficits are discussed later in more detail. In addition, the quality of relationship might also affect the rating of the patient or the caregiver (Clare, Nelis, Martyr, Roberts, et al., 2012; Huang, Chang, Tang, Chiu, & Weng, 2009).

The last section to multifactoriality of rating discrepancy presents empirical findings and methodological issues on the distinction between positive and negative rating discrepancies, considering that positive and negative rating discrepancies might represent two distinct aspects of rating discrepancy.

### **2.3.1 Impaired Awareness of Deficits in Alzheimer's Disease**

Clare, Nelis, Martyr, Markova, et al. (2012) defined awareness as "a reasonable or realistic perception or appraisal of a given aspect of one's situation, functioning or performance, and/or of the resulting implications" (p. 566). Different terms have been used to refer to impaired awareness of deficits in AD, such as anosognosia, denial, and loss of insight (Starkstein, 2014).

The prevalence of impaired awareness of deficits is reported to range between 20% and 80% (Starkstein, 2014). This wide range may be due to variability of diagnostic factors, the sample, the domain, and the theoretical background. Impaired awareness of deficits occurs already in patients with mild AD (Hardy, Oyebode, & Clare, 2006; Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996; Vogel et al., 2010) and there is empirical evidence that it becomes more impaired as dementia progresses (Starkstein, 2014; Vogel, Waldorff, & Waldemar, 2015). The aetiology of unawareness in mild AD has yet been not enlightened in detail, but there is agreement that it is based on a complex multifactorial construct. The biopsychosocial approach by Ownsworth, Clare, and Morris (2006) proposes a relative and interactive influence of neurocognitive, psychological, and socio-environmental factors for explaining awareness of AD related symptoms. The biological level contains neurological and neuropsychological theories of awareness and assumes that unawareness is often attributable to brain damage (Robertsson, Nordstrom, & Wijk, 2007). Right frontal, right parietal, as well as right and left medial temporal lobes and the orbitofrontal cortex are emphasized in relation to unawareness (Sedaghat et al., 2010). On the psychological level, defence mechanisms, coping strategies, pre-illness personality factors, and adjustment are considered (Ownsworth et al., 2006; Robertsson et al., 2007; Seiffer, Clare, & Harvey, 2005). The socio-environmental factors concern the interaction between the patient and his or her relatives, friends, or caregivers with the context and communication as essential concepts. These include dimensions of experience such as stigma or exclusion, and the influence of social and cultural representations of dementia (Ownsworth et al., 2006; Robertsson et al., 2007).

For assessing awareness of deficits in AD, three main strategies have become established: the clinician rating, the prediction of performance discrepancy strategy, and the patient-caregiver discrepancy strategy (Clare, 2004; Leicht & Gertz, 2009; Starkstein, 2014). The patient-caregiver discrepancy strategy is based on discrepancy scores, hence impaired awareness is assumed if the rating of a deficit or the suffering by the caregiver is higher than

the patient's rating. Even if validity and reliability of this strategy have been demonstrated (Sato et al., 2007; Starkstein, Jorge, Mizrahi, & Robinson, 2006a) literature shows that rating discrepancy contains more than just impaired awareness of deficits (Ready, Ott, & Grace, 2006). For instance, caregivers' report may be influenced by caregiver characteristics (see the next section) (Chang, Edwards, & Lach, 2011; Clare, Nelis, Martyr, Roberts, et al., 2012; Schulz et al., 2013).

### **2.3.2 Caregiver Rating Bias**

The over-reports of the patients' suffering by the caregivers has been called *caregiver rating bias* (Schulz et al., 2013). Caregiver burden is one of the most reported predictors of caregiver rating bias (Burke et al., 1998; Chang et al., 2011; Clare, Nelis, Martyr, Roberts, et al., 2012; Sands et al., 2004). There is some evidence that caregiver depression also leads to caregiver rating bias, but that it might play a less significant role (Conde-Sala et al., 2013; Jorm et al., 1994; Karlawish, Casarett, Klocinski, & Clark, 2001; Schulz et al., 2013). Caregiver burden and depression can be considered as two separate variables. Caregiver burden is defined as a reaction to the physical, emotional, economical, and social costs of the caregiving relationship, while caregiver depression is a mood disturbance triggered by the stress of providing care and manifested by feelings of loneliness, isolation, fearfulness, and being easily annoyed (Pinquart & Sörensen, 2003). Demographics of the caregiver might also bias their ratings (Clare, Nelis, Martyr, Roberts, et al., 2012).

### **2.3.3 Direction of Rating Discrepancy**

According to Snow et al. (2005) there are three approaches to evaluate the amount and direction of rating discrepancy between the patient and caregiver ratings (the amount of response discrepancy is an indication of response precision, the direction of response discrepancy is an indication of response bias):

1. A raw discrepancy score (patient - caregiver score) or a standardized discrepancy scores  $((\text{mean patient} - \text{caregiver score}) / \text{SD})$
2. The percentage bias  $((\text{caregiver} - \text{patient score}) / \text{patient or caregiver score}) \times 100$
3. General linear model (e.g., linear regression, MANOVA) in which a discrepancy variable is the dependent variable predicted by independent variables which are factors hypothesized to affect the discrepancy

The majority of research on rating discrepancies has addressed the amount of the rating discrepancy using raw or standardized discrepancy scores. A few studies have focused on the distinction between negative rating discrepancies in which patients' ratings are lower than the ratings of the caregivers and positive rating discrepancies in which caregivers rate the deficits lower than the patients (Arguelles, Loewenstein, Eisdorfer, & Arguelles, 2001; Novella et al., 2001, 2006; Smyth et al., 2002; Tabert et al., 2002; Tay et al., 2014). A study that examined the predictive utility of rating discrepancy in functional deficits found that a negative rating discrepancy index score was the best predictor of the conversion from MCI to AD, whereas the magnitude of the rating discrepancy and the informant reported deficits had less and self-reported deficits had no predictive value (Tabert et al., 2002).

According to Tay et al. (2014) positive and negative rating discrepancies could reflect distinct underlying processes, since predictors may vary depending on the direction of rating discrepancy in QoL. This suggests that using a linear regression model with the amount of rating discrepancy (including positive and negative rating discrepancies as a continuum) as the dependent variable might distort the results. Considering the direction of the rating discrepancy in regression models could therefore raise the quality of the results and might provide more insight into rating discrepancies. This could for instance be provided by a

binary logistic regression analysis, or controlling the linear regression analysis for the direction of the discrepancy.

## **2.4 Domain Specificity of Rating Discrepancy**

Studies which compared rating discrepancies of different domains showed that they vary in their magnitude across domains (Green, Goldstein, Sirockman, & Green, 1993; Leicht et al., 2010; Magaziner, Zimmerman, Gruber-Baldini, Hebel, & Fox, 1997; Vasterling, Seltzer, Foss, & Vanderbrook, 1995). Rating discrepancies seem to be greatest for recent memory, ADL, and apathy, moderate for anxiety, irritability, and attention, and minimal for remote memory, physical health, and depression (Green et al., 1993; Leicht et al., 2010; Magaziner et al., 1997; Novella et al., 2001; Vasterling et al., 1995). There is evidence that agreement is higher for measures that are directly observable, i.e. when questions concern behaviours, functions, diagnoses, conditions, and signs and symptoms with observable manifestations (Magaziner et al., 1997; Novella et al., 2001).

Likewise, analysing possible caregiver predictors of discrepancy scores leads to the assumption that there exist domain specific patterns. Rosenberg, Mielke, and Lyketsos (2005) and Teri and Truax (1994) showed that caregiver burden and depression contribute to caregiver ratings of patients' depressive symptoms. For QoL, the domain with the most numerous and most current studies, there is agreement that caregiver burden is a strong predictor of dyadic rating discrepancy (Conde-Sala, Garre-Olmo, Turro-Garriga, Lopez-Pousa, & Vilalta-Franch, 2009; Karlawish et al., 2001; Sands et al., 2004; Schulz et al., 2013). Caregiver depression, however, was seen as tending to play a less significant role in the dyadic rating discrepancy of QoL (Karlawish et al., 2001; Schulz et al., 2013). Clare, Nelis, Martyr, Roberts et al. (2012) demonstrated that caregiver burden was associated with discrepancies in rating memory and ADL but not social functioning; caregiver depression was not addressed.

One should take into consideration, however, that beside domain specificity, other factors also affect rating discrepancies, including characteristics of the construct and the assessment methods (Neumann, Araki, & Gutterman, 2000; Novella et al., 2006).

#### **2.4.1 Rating Discrepancy in Apathy**

There is a lack of studies concerning rating discrepancy between self- and caregiver ratings in apathy. Consistent with rating discrepancies in other domains, patients' and caregivers' reports of apathy diverge significantly, with a tendency to overestimation on the part of the caregiver, i.e. caregivers generally report more apathy than patients themselves (Leicht et al., 2010; Robert et al., 2002). To my knowledge, no study until now has evaluated predictors of dyadic rating discrepancy in apathy.

Investigating rating discrepancy in apathy is of major importance for the following reasons. First, apathy is one of the most frequent and persistent neuropsychiatric symptom in AD (Brodaty et al., 2015; Di Iulio et al., 2010). Second, apathy measures are based often on self- and/or caregiver reports to the clinician, who weights the ratings in relation to his or her knowledge (Clarke et al., 2011; Starkstein et al., 2010). Third, patients with impaired awareness are more apathetic (Horning, Melrose, & Sultzer, 2014; Starkstein et al., 2010) and finally, apathy is associated with caregiver burden and fewer positive experiences in caregiving (Brodaty & Burns, 2012; Meiland, Kat, van Tilburg, Jonker, & Dröes, 2005; Onyike et al., 2007). An early occurrence of apathy in mild AD leads to increased reliance on caregivers to initiate activities that the patient is actually capable of performing alone. Caregivers who lack an understanding of apathy as an integral part of AD, may misinterpret apathetic patients to be withdrawn, insensitive, disinterested, lazy, uncaring, or deliberately oppositional (Colling, 2004). This corresponds to the equity theory, which postulates that a perceived imbalance between give and receive, could cause stress in the individuals who subjectively invest more than they receive (DeMaris, 2010). This, in turn, could lead to

caregiver burden and to a distortion of their perception of apathy symptoms and subsequently to a rating of a higher severity of apathy symptoms.

## **2.5 The Longitudinal Course of Rating Discrepancy**

The few studies, which have investigated the longitudinal course of rating discrepancy, report divergent results. On the one hand rating discrepancies in memory functioning, everyday activities, social functioning, and marital relationship quality remained stable over 20 months (Clare, Nelis, Whitaker, et al., 2012). On the other hand Josep L Conde-Sala, Turró-Garriga, Garre-Olmo, Vilalta-Franch, & Lopez-Pousa (2014) were able to show an increase of rating discrepancies within 36 months in QoL. This difference could be due on different levels of cognitive state, time intervals, or domains. The increasing severity of dementia might lead to greater rating divergence.

Clare, Nelis, Martyr, Whitaker, et al. (2012) evaluated longitudinal course of patient and caregiver ratings and rating discrepancies of memory functioning, everyday activities, social functioning in mild dementia. They reported for memory functions no change in self- and informer ratings, a significant increase in self- and informer ratings of everyday activities and stability in the self-rating and an increase of the caregiver rating of social functioning. This indicates domain specificity in the longitudinal development of self- and caregiver ratings. Furthermore there are indications to consider patient and caregiver ratings separately in exploring the longitudinal course of rating discrepancies.

Paper 3 investigated the process and effect of a multicomponent cognitive-behavioural treatment on impaired awareness of apathy. Therefore the next section focus on impaired awareness of deficits and psychotherapy.

### **2.5.1 Impaired Awareness of Deficits and Psychosocial Interventions**

To date, there are no randomized controlled trials of psychosocial treatments affecting impaired awareness of deficits in AD (Clare, Marková, Roth, & Morris, 2011; Starkstein, 2014). Studies on change of awareness by a treatment in other diseases reported mixed results (Connolly Gibbons et al., 2007). Schrijnemaekers et al. (2014) give an overview of treating unawareness in patients with acquired brain injury. They concluded that impaired awareness of symptoms could be improved through a combination of education and multimodal feedback related to performance.

Treatments that target awareness, however, might be recommended for several reasons. Various researchers demonstrated a positive correlation between impaired awareness and neuropsychiatric symptoms as well as caregiver burden (Aalten et al., 2006; Horning et al., 2014; Starkstein, 2014; Turró-Garriga et al., 2013; Vogel et al., 2010). Furthermore, unawareness may increase morbidity with respect to the following factors: delayed contact with healthcare providers, an adverse effect on safety, a diminishment of medication compliance, and the disuse of compensatory strategies (Barrett, Eslinger, Ballentine, & Heilman, 2005). Therefore, raising awareness could influence all these outcomes and enlarge the repertoire of behaviours toward self and others, which in turn can have an effect on the success of a treatment (Grosse Holtforth et al., 2007; Schönberger, Humle, & Teasdale, 2006).

Conversely, targeting awareness could have an adverse effect on the patients. Previous studies reported a positive correlation between awareness and depression (Aalten et al., 2006; Horning et al., 2014), or dysthymia (Vogel et al., 2010). An impairment of awareness is suggested to be an emotional response to the disease and its impairments in the fashion of a protection (Aalten et al., 2006; Horning et al., 2014; Vogel et al., 2010). Addressing impaired awareness, possibly a continuing protective factor, through a treatment could disrupt the



whole system and raise emotional distress. Findings indicate, nevertheless, that the process of developing awareness of deficits during rehabilitation is not associated with heightened emotional distress (Ownsworth & Clare, 2006).

A few researchers have analysed reduced awareness of deficits as a predictor of the outcome of cognitive interventions in AD and suggest that impaired awareness may limit therapeutic outcome (Clare et al., 2004; Fernandez-Calvo et al., 2015; Koltai et al., 2001). But little is known about factors that mediate the relationship between impaired awareness and therapeutic outcome. For instance, psychological factors such as denial, coping or personality or social factors such as stigma, exclusion, and social desirability, could complicate the therapeutic work and consequently impair the therapeutic outcome (Ownsworth et al., 2006). Otherwise, a trusting therapeutic relationship could provide a secure environment for the patient that may allow an individual to overcome these defence mechanisms and may thus enhance patient compliance in therapy, which is a prerequisite for therapy success (Schonberger et al., 2006).

## 3 THE PRESENT THESIS

### 3.1 Aims of the Thesis

As mentioned in the introduction, there are several indications of domain specificity in rating discrepancy. In particular the magnitude, the predictors, and the longitudinal course of rating discrepancies seem to differ across domains. As studies concerning patient-caregiver rating discrepancy in apathy are not only under-represented in literature but are also of great importance, the main purpose of the present thesis was to examine multifactoriality, domain specificity, and the temporal course of rating discrepancy in apathy. Figure 1 shows a graphic representation of the aims of the three empirical studies. The more specific research questions are as follows.

**Multifactoriality:** Several major components of rating discrepancy were addressed in the present thesis with a special focus on the caregiver rating bias and the direction (over- vs. underestimation) of the rating discrepancy with the following research questions:

- Do caregiver burden and/or caregiver depression predict apathy rating discrepancy (Paper 1)?
- Do aspects of the patient-caregiver relationship predict apathy rating discrepancy (Paper 1)?
- Are positive and negative rating discrepancies different constructs (Paper 2)?

**Domain Specificity:**

- Do rating discrepancies of depression, apathy, ADL, and QoL differ in their magnitude (Paper 1)?
- Do rating discrepancies of depression, apathy, ADL, and QoL differ regarding their predictor structure (Paper 1)?

- Are rating discrepancy of apathy and impaired awareness of AD measured by a clinical rating affected differently by a psychosocial treatment (Paper 3)?

#### **Longitudinal Course:**

- In which ways do rating discrepancy, and patient and caregiver apathy ratings change across time (Paper 2)?
- In which ways are rating discrepancy and the patient and caregiver apathy ratings affected by a psychosocial multicomponent treatment or a treatment as usual (Paper 3)?
- Do positive or negative rating discrepancies predict clinical apathy at follow-up (Paper 2)?

The next three sections summarize the main findings of each paper and answer the questions specified above.

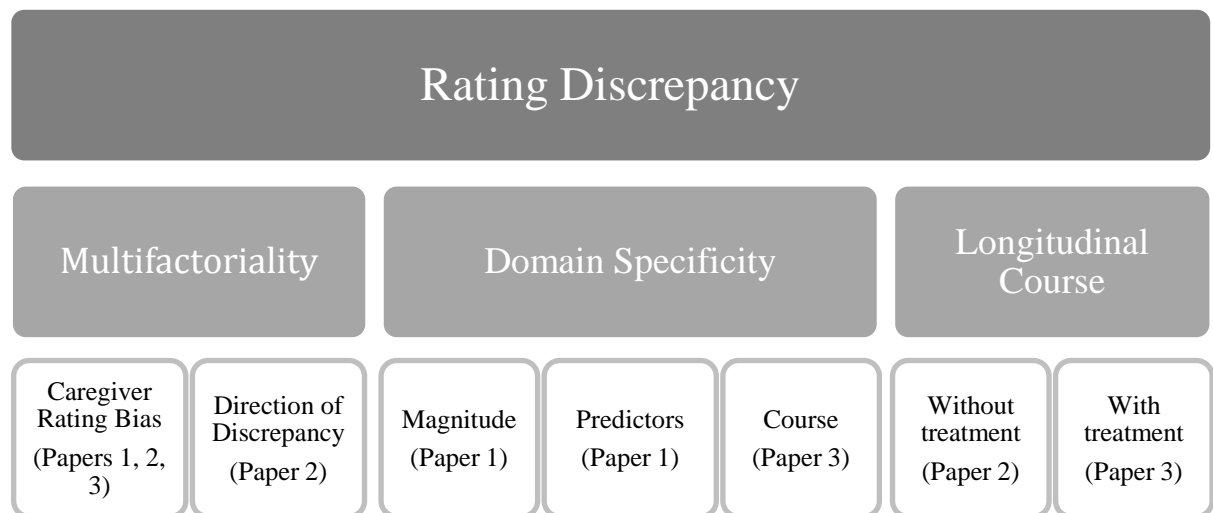


Figure 1. Graphic representation of the aims of the thesis.

### **3.2 Summary of Paper 1: ‘Caregiver rating bias in mild cognitive impairment and mild Alzheimer’s disease: Impact of caregiver burden and depression on dyadic rating discrepancy across domains’**

#### **Background and Objectives**

Caregiver burden is the most widely used caregiver variable for explaining dyadic rating discrepancy and appears to contribute to the caregiver rating bias in various domains (Burke et al., 1998; Chang et al., 2011; Clare, Nelis, Martyr, Roberts, et al., 2012; Schulz et al., 2013). Additionally, there is some evidence that caregiver depression also leads to caregiver rating bias, but that it might play a less significant role (Conde-Sala et al., 2013; Karlawish et al., 2001; Schulz et al., 2013). The main purpose of Paper 1, therefore, was to examine domain-specific relationships between caregiver burden or depression and dyadic rating discrepancies of depression, apathy, ADL, and QoL.

#### **Methods**

The sample of the cross-sectional study consisted of 202 persons: 60 with MCI, 41 with mild AD, and 101 caregivers. Data were derived from the study entitled ”Motivational Reserve as a Protective Factor in Mild Alzheimer’s Dementia and Mild Cognitive Impairment” (MoReA).

#### **Results**

All domains showed on average negative rating discrepancies, which indicate that either the patients underrated their own suffering, that the caregivers overestimated it, or both. The statistical magnitude of these biases, defined by the effect size  $d$ , was low for depression ( $d = 0.33$ ) and moderate for apathy ( $d = 0.65$ ), daily functioning ( $d = 0.49$ ), and QoL ( $d = 0.54$ ). Caregiver burden significantly contributed to explaining patient-caregiver rating discrepancies in apathy, daily functioning, and QoL. Depression discrepancy seems to be predicted by both,

caregiver burden and depression. The type of relationship (spouses vs. others) did not predict any dyadic rating discrepancy.

## **Discussion**

In accordance with previous literature, dyadic rating agreement on apathy, daily functioning, and QoL was poor (Farias, Mungas, & Jagust, 2005; Leicht et al., 2010; Sands et al., 2004; Schulz et al., 2013) and moderate on depression (Leicht et al., 2010; Vasterling et al., 1995). The data revealed that caregiver burden is a more important predictor of caregiver rating bias than caregiver depression. Hence, the caregiver rating bias can be attributed to caregiver burden, i.e. to the demanding situation to which caregivers are exposed. According to Zanetti et al. (1999) caregivers' judgements were especially influenced by demands and restrictions on caregivers' time. When caregiver burden is present, data, based on caregiver ratings, should therefore be interpreted with caution.

Rating discrepancies seem to reflect a combination of patients' underrating their deficits and caregivers' overestimating the patient's deficits. Furthermore, the findings show domain-specific patterns. As the predictor structure differs in relation to the domain, it is not possible to generalize the influence of caregiver burden and depression on rating discrepancies across domains.

### **3.3 Summary of Paper 2: ‘Caregiver perception of apathy in patients with mild cognitive impairment and Alzheimer’s disease: a longitudinal study’**

#### **Background and Objectives**

The purpose of Paper 2 was to examine longitudinally dyadic rating discrepancy as well as patients’ and caregivers’ apathy ratings in MCI and mild AD. As shown in Paper 1, increased burden may lead to endorsing more severe apathy symptoms in cognitively impaired patients; burdened caregivers seem to be less tolerant of patients’ suffering than the patients themselves. Esposito et al. (2014) emphasized the importance of giving positive feedback and setting specific performance goals that are attainable in the patient’s environment. Hence, caregiver under-reports and over-reports could be interpreted as efficacy judgements; they may reflect how greatly caregivers support patients’ efforts and how greatly they believe in patients’ abilities, which could have an impact on the course of patients’ apathy. Therefore, a particular focus was on the distinction between the positive and negative caregiver bias and its predictive value for a clinical diagnosis of apathy.

#### **Methods**

Paper 2 was based on baseline and follow-up data of the MoReA Study and drew on a sample of 92 dyads (MCI:  $n = 54$ , AD:  $n = 38$ ). As the type of diagnosis (MCI/AD) does not affect discrepancy in rating apathy (see Paper 1), I did not run analyses separately for both diagnoses. Dyads were categorized depending on whether the caregiver reported fewer deficits (positive caregiver bias) or more deficits (negative caregiver bias) than the patient did.

#### **Results**

Caregiver apathy ratings and rating discrepancy showed a significant increase within 12 months. By contrast, patient and clinician ratings showed no changes across the two time points. Ratings with a negative caregiver bias remained stable, while those with a positive

caregiver bias showed a significant increase in the caregiver ratings but also a significant decrease in the patients' ratings. A negative caregiver bias at baseline was significantly related to greater likelihood of having clinical apathy at follow-up.

## **Discussion**

The findings and previous literature highlight the necessity to consider the development of self- and informer ratings separately, instead of change in rating discrepancy (Clare, Nelis, Whitaker, et al., 2012; Conde-Sala et al., 2014). Positive and negative caregiver bias should be distinguished, moreover, as they seem to reflect distinct dyadic processes (Tay et al., 2014). No changes were detected over the follow-up period in the group with a negative caregiver bias. By contrast, the group with a positive caregiver bias showed a significant increase in the caregiver ratings but also a significant decrease in the patients' ratings. Rating discrepancy here approaches zero, which suggests that there may be some adjustment in perception of apathy, possibly resulting from experiences in everyday life or a better understanding of the illness.

The finding that negative caregiver bias predicts clinical apathy at follow-up could reflect on the one hand the caregivers' diagnostic or prognostic abilities, based on knowledge of the patient's past and present functional abilities. On the other hand, these abilities may reflect efficacy judgements as a predictor of a clinical outcome. Regardless of whether caregivers are accurate or biased in their perceptions, negative rating discrepancies can be interpreted as a risk factor for developing apathy.

### **3.4 Summary of Paper 3: ‘Impaired awareness of apathy in mild Alzheimer’s disease: process and effect of a multicomponent cognitive-behavioural treatment’**

#### **Background and Objectives**

Earlier research has shown that impaired awareness of deficits in AD may limit therapeutic outcome, but it remains unclear how awareness is associated with the therapeutic process and if awareness is changeable through a psychosocial intervention (Clare, Wilson, Carter, Roth, & Hodges, 2004; Fernández-Calvo et al., 2015; Koltai, Welsh-Bohmer, & Schmechel, 2001). Hence, the process and the effect of a multicomponent CBT were examined in relation to impaired awareness of apathy, assessed by a patient-caregiver discrepancy score.

#### **Methods**

Paper 3 is based on baseline and post-intervention data from the longitudinal randomized controlled trial, the ‘Cognitive-behavioural treatment for patients with mild AD and their caregivers’ (CBTAC) (Forstmeier, Maercker, Savaskan, & Roth, n.d.). Participants of the CBT group ( $n = 17$ ) received a treatment comprising different modules (see Table 11) that targeted reduction of neuropsychiatric symptoms. They rated the therapeutic process after every session. The comparison group ( $n = 12$ ) received a treatment as usual (TAU). Awareness of apathy was based on the rating discrepancy in apathy. Additionally, a clinical rating of impaired awareness of AD symptoms was used.

#### **Results**

Regarding the relationship between impaired awareness and the therapeutic process perceived by the patients, impaired awareness of apathy correlated significantly with global alliance ( $r = -.747, p = .007$ ). In addition, the findings showed a confidence interval overlap of



only 0.1 for the module psychoeducation and cognitive restructuring regarding the association of awareness and self-esteem. Furthermore, the subscale ‘bond’ in couples counselling differed significantly from the remaining modules; there was an outstanding negative correlation between impaired awareness in apathy and ‘contentment with bond’. Awareness of apathy remained stable in the CBT condition and decreased significantly in the control condition. This change can be attributed to an increase in the patients’ apathy ratings, whereas the caregiver ratings remained stable over time. Impaired awareness of AD symptoms did not show time x group interactions.

## **Discussion**

The results indicate that the therapist should consciously deal with aspects of the relationship and should invest more effort to establish a therapeutic alliance in treating patients with impaired awareness and preferably use a more individual approach. Furthermore, under the assumption that a rating discrepancy corresponds to impaired awareness, the present study provides preliminary support for increasing awareness of apathy via TAU. Nevertheless, stabilization of apathy in the CBT condition in the face of disease progression, also may indicate that the treatment is beneficial, even without evidence of improvement (Brodaty & Burns, 2012). Hence, it remains unclear whether these effects result from a change in awareness of apathy or a change in apathy symptoms.

In conclusion, the findings of the present study pave the way for future research on awareness in relation to interventions in AD and suggest that it may be of real benefit to consider the level of awareness in treating individuals with AD.

## 4 GENERAL DISCUSSION

In the following sections, the findings of the three research papers will be integrated in an overall discussion to draw general conclusions and to provide ideas for future research. Finally, implications for research and clinical practice will be given. The main focus of the discussion is on investigating the contribution of the three papers to multifactoriality, domain specificity, and the longitudinal course of rating discrepancies in apathy.

### 4.1 Multifactoriality of Rating Discrepancy

This section discusses two different aspects of rating discrepancy. First, an explanatory approach for the caregiver rating bias will be presented along with a special focus on discussing apathy. Second, the findings of Paper 2 will be discussed regarding the direction of the rating discrepancy, considering the longitudinal course of positive and negative rating discrepancies in apathy.

#### 4.1.1 An Explanatory Approach for the Caregiver Rating Bias

The present thesis and previous research showed that rating discrepancy is a multifactorial construct comprising, among others, characteristics of the caregiver. Paper 1 addressed predictors of rating discrepancies of different domains and revealed that caregiver burden is a more important predictor of caregiver rating bias than caregiver depression. Hence, the caregiver rating bias can be attributed to caregiver burden. Several recent studies have replicated this finding (Conde-Sala et al., 2013, 2014; Dourado et al., 2014; Gomez-Gallego, Gomez-Garcia, & Ato-Lozano, 2015; Orgeta, Orrell, Hounscome, & Woods, 2015). Until now, a theoretical approach explaining the caregiver rating bias has not been provided.

To explain impaired awareness of patients in early-stage dementia, Clare et al. (2011) defined a theoretical framework consisting of three main levels: performance monitoring in

relation to selected tasks, evaluative judgements about aspects of functioning, and meta-cognitive reflections, as in relation to the impact and implication of the condition. This theoretical framework could be transferred from impaired awareness by the patient to the caregiver rating bias as follows:

- First level, “Monitoring”. The caregiver monitors the performance of the patient.
- Second level, “Evaluation and Judgement”. The caregiver evaluates and judges the performance.
- Third level, “Impact and Implications”. The caregiver reflects the performance on a meta-cognitive level, in which he or she considers the impact and implication for his or her condition as a caregiver.

Epstein, Hall, Tognetti, Son, and Conant (1989) presented explanations for caregiver rating bias. These explanations can be embedded in the three levels of this theoretical framework and linked to caregiver burden in apathy.

First level: Emotions and attitudes may be selectively revealed by the patients, in other words, negative feelings and opinions may be more likely to be displayed than positive ones. Caregivers would therefore infer more overall negativity than the subject actually experiences (Epstein et al., 1989). In apathy, burdened caregivers might misinterpret patients’ lack of motivation and put pressure on the patients and criticize them for being lazy. In turn, these patients become more withdrawn and passive and consequently show a more pronounced apathetic behaviour (Colling, 2004).

Second level: Epstein et al. (1989) state that:

There is a documented tendency for observers to give more weight to negative than positive information when forming impressions of others, and to be biased by highly salient events when making any generalization about social phenomena. Negative expressions, such as weeping or complaining, are surely more salient (and memorable)

than more positive ones. Therefore, even if subjects revealed their negative and positive feelings equally, proxies' impressions would be more influenced by the negative, with the result that their opinions of the subjects' condition would be biased negatively. ( p. 97)

In apathy, the caregivers might perceive particularly the diminished goal-directed behaviour, cognition, and emotions of the patient and take less notice of components that are still maintained because the former is more disturbing and therefore more salient. This effect could be more pronounced in burdened caregivers as they have a reduced capacity to cope with the demanding situation or use dysfunctional coping strategies (Zucchella, Bartolo, Pasotti, Chiapella, & Sinforiani, 2012).

Third level: Caregivers might feel a need to justify the time they spend helping and do so by exaggerating the debilities of those whom they help (Epstein et al., 1989). Especially burdened caregivers might transfer their own feelings of worry, frustration, fear, etc. into their ratings, inducing an overestimation of the patient's condition (Ready, Ott, & Grace, 2004; Sands et al., 2004). Paper 2 provides indirectly an indication that caregiver confidence could be reduced in a burdened caregiver, as the caregiver-rated self-efficacy of the patients was significantly higher in the group with positive than with negative rating discrepancy. Further, according to Lyons, Zarit, Sayer, & Whitlatch (2002) caregivers might anticipate future problems about providing care into the rating. A recent study revealed that the relationship between caregiver burden and their ratings of neuropsychiatric symptoms was mediated by the caregivers' use of disengagement coping strategies that might lead them to believe they do not have the ability to address or process problems (García-Alberca et al., 2014). Hence burdened caregivers might be more pessimistic about future implications of their lives and the relationship to the patients, as an early occurrence of apathy in MCI or mild AD leads to increased reliance on caregivers to initiate activities that the patient is actually capable of performing alone. This could also explain, why caregivers did not notice a change in apathy

symptoms initiated by the interventions in Paper 3. Burdened caregivers could be rather focused on the impact and implications of apathy and neglect the current state as well as not notice the behavioural gains achieved by the patients. This is also in line with Stella et al. (2015) who suggest that caregivers of patients with mild AD especially have incomplete perception of the patients' neuropsychiatric symptoms.

To sum up, all three levels of the presented transferred theoretical framework (Clare, Whitaker, et al., 2011) can explain the caregiver rating bias in apathy, but there is evidence that the third level seems to be of greater significance. The model assumptions, on which level of the model and in what way caregivers of apathetic patients with mild AD are biased by burden, should be clarified in further studies.

#### **4.1.2 The Distinction between Positive and Negative Rating Discrepancies**

Paper 2 contributed to the evidence that positive and negative rating discrepancies reflect distinct underlying processes and that aggregate data neglects information that could be important in understanding rating discrepancies.

The findings showed different patterns of temporal development. The group with a negative rating discrepancy showed no changes over the follow-up period. By contrast, the group with a positive rating discrepancy showed not only a significant increase in the caregiver ratings, but also a significant decrease in the patients' ratings. Rating discrepancy here approaches zero, which suggests that there may be some adjustment in perception of apathy, possibly resulting from experiences in everyday life or a better understanding of the illness.

Furthermore, Paper 2 displayed that a negative rating discrepancy was significantly related to greater likelihood of being diagnosed with apathy at follow-up (OR = 17.8). This is in line with Tabert et al. (2002) who reported that a negative discrepancy score in functional deficits predicted the conversion from MCI to AD within two years (OR = 7.9).

There are different explanations for this finding. First, it could reflect the caregivers' diagnostic or prognostic abilities, based on knowledge of the patient's past and present functional abilities. There is considerable evidence that caregivers are a valuable source in apathy diagnosis and have a good predictive validity (Clarke et al., 2007; Dujardin et al., 2008; Marin, 1991). Second, Starkstein et al. (2010) found that apathy in AD (based on caregiver ratings) is significantly predicted by impaired awareness. Therefore, impaired awareness as an aspect of the negative rating discrepancy might have predicted the clinical apathy diagnosis at follow-up too. Moreover in the study by Tabert et al. (2002), informant reported, but not self-reported, functional deficits predicted time to conversion from MCI to AD, which suggests that both explanations are possible. Third, as already mentioned in the section above, in Paper 2 solely caregiver ratings of patient's self-efficacy differed significantly with regard to the positive and negative rating discrepancy, which indicates that the caregivers' judgement of the patients' efficacy is predictive for occurrence of clinical apathy within a year. This is in line with Rohrbaugh et al. (2004), who demonstrated that spousal perception of patients' efficacy in coping with the disease predicted patient survival, independent of patients' self-efficacy judgements in congestive heart failure patients. Thus, caregivers who are confident and tend to minimize difficulties on the part of the patient could have a positive impact on the occurrence of apathy. A previous study on motivational processes in depression found self-efficacy to be a mediator between social support and depression in cognitively impaired individuals (Fankhauser, Drobetz, Mortby, Maercker, & Forstmeier, 2014). Its authors discussed social support in the form of coping assistance, i.e. providers of social support help the receiver cope successfully with stressful situations. Additionally, burdened caregivers might put pressure on the patients and criticize them, and consequently patients become increasingly withdrawn and passive (Colling, 2004). Besides, an over-abundance of social support can lead to more sadness, frustration and finally result in decreased well-being of the patients. The apathetic person might feel unable to reciprocate

received support, which can lead to feelings of inferiority (Gleason, Iida, Shrout, & Bolger, 2008) or even an aggravation of apathy. Future studies are needed to examine the relationship between caregivers' perception of apathy and patients' motivational abilities.

Recently published studies have also supported the need to distinguish between positive and negative rating discrepancies. They evaluated predictor structure and reported an association between patients' depression and positive rating discrepancy (i.e. caregivers rate the symptoms lower than the patients) (Gomez-Gallego et al., 2015; Smeets et al., 2014; Tay et al., 2014). These findings suggest that depression and impaired awareness act as counterparts on rating discrepancy, like two opposite biases (Mograbi & Morris, 2013).

Various strategies for distinguishing positive and negative rating discrepancy have been used. In Paper 2 and in some other studies, rating discrepancies were categorized depending upon whether they were greater or less zero (Smeets et al., 2014; Tabert et al., 2002; Tay et al., 2014). For others, just a mean difference score significantly different from zero, using a paired student's *t*-test, provided evidence of systematic bias (Boyer, Novella, Morrone, Jolly, & Blanchard, 2004; Novella et al., 2001). In a third study, the distinction was based on the residuals of the regression equation of patients' ratings on caregivers' ratings (Gomez-Gallego et al., 2015). The use of different approaches could lead to varying findings, thus it is of great importance to create a gold standard in calculating rating discrepancies in general and for the distinction of positive and negative rating discrepancies. Since discrepancies close to zero could also be considered as in agreement, further methodological studies are necessary to evaluate the intersection between agreement and bias.

In conclusion, the findings of the present thesis emphasize the importance of distinguishing between positive and negative rating discrepancies. The findings of analyses that include the magnitude but do not consider the direction of the rating discrepancies might be distorted.

## 4.2 Domain Specificity of Rating Discrepancy

The findings of Paper 1 and Paper 3 support the assumption of domain specificity in rating discrepancies in different ways. First, in Paper 1 rating discrepancies of depression, apathy, ADL, and QoL differed with respect to their magnitude. Intraclass correlation coefficients (ICC) of apathy (.38), daily functioning (.38), and QoL (.30) were low, and those of depression, moderate (.49). This is in line with previous studies, which suggest a similar magnitude in apathy and ADL, and more agreement for depression patient-caregiver ratings (Leicht et al., 2010; Vasterling et al., 1995). Hence, there is evidence that symptoms of depression are perceived and rated by the patient and caregiver more similarly than apathy symptoms and ADL. Some domains might be more salient for both the patients and the caregiver, and offer the opportunity for more observation or feedback. Besides the observability, the objectivity of the questions is related to the agreement of patient and caregiver ratings. The questions need to be easily understood by those providing responses (Magaziner et al., 1997). Characteristics of the construct and the assessment methods, however, could also lead to different magnitudes in rating discrepancies (Neumann et al., 2000; Novella et al., 2006; Perkins, 2007). Bosboom et al. (2012) showed, for instance, different predictor structure depending on whether the caregiver rated the item from the caregiver-caregiver perspective (the caregiver rates the scale as they see it) or the caregiver-patient perspective (the caregiver rates the scale as they believe the patient would rate it). In Paper 1 the assessment of depression is based on the Geriatric Depression Scale (Yesavage et al., 1986), a 2-point scale, termed in absence/presence items, while the other measurements consist of rating dimensions with larger response scales. This difference could also explain the divergence between the rating discrepancies of depression and the remaining modules in Paper 1; the smaller Likert-scale might have a higher probability of agreement or the level of agreement is higher, when questions are framed in terms of absence/presence than a rating



dimension. To prevent scaling effects distorting measurement when calculating discrepancy scores, the differences could have been divided by their means, or more specifically to correct raw discrepancy scores, to account for the effect of numerical differences on overall level of scoring by dividing the discrepancy score by the mean of the patient and caregiver score (Clare, Nelis, Whitaker, et al., 2012).

Second, the predictor structure differed in relation to the domains in Paper 1, hence it is not possible to generalize the influence of different factors on rating discrepancy. This indicates heterogeneity and the existence of different causes of rating discrepancies, depending on the domain. Recently, Dourado et al. (2014) developed a multidimensional scale based on patients' and informants' reports, including the domains of cognitive deficits, family and social relationships, and ADL. The authors confirmed the findings of Paper 1 regarding different associations between rating discrepancies and clinical variables depending on the domain. In addition, Sousa et al. (2015) approved the relative independence between rating discrepancies of different domains as suggested in Paper 1.

Third, the findings of Paper 3 suggest domain specificity in relation to the treatment, since rating discrepancy in apathy, but not the clinical insight rating, showed an effect of treatment. Additionally, the results showed a marginally significant correlation between awareness of apathy measured by a rating discrepancy and a clinical rating of awareness of AD related deficits ( $r = .34, p = .070$ ). Domain specificity could also explain why in a recent study, impaired awareness of symptoms of AD assessed by the Clinical Insight Rating was not found to be a significant predictor of patient-caregiver discrepancy ratings in QoL (Gomez-Gallego et al., 2015).

The question is raised if rating discrepancy is domain specific per se or if differences are based on the domain specificity or methodological variance of significant predictors, i.e. impaired awareness or caregiver burden. Mograbi et al. (2015) reported varying predictor

structures of the performance discrepancy and patient/informant discrepancy strategies in memory functions, hence concerning the same domain. Thus, there is evidence that different strategies of assessment reflect distinct facets of impaired awareness. The domain specificity could also result from different degrees of deficits (Dourado et al., 2014; Leicht et al., 2010). In Paper 2 it becomes apparent that most of the persons diagnosed with apathy, i.e. patients with more pronounced apathy symptoms, belonged to the group with a negative rating discrepancy, that is, with larger negative discrepancy scores. Hence, differences in rating discrepancies between domains rather reflect the circumstances that the deficits are pronounced differently in mild AD, than domain specific patterns of impaired awareness or caregiver burden.

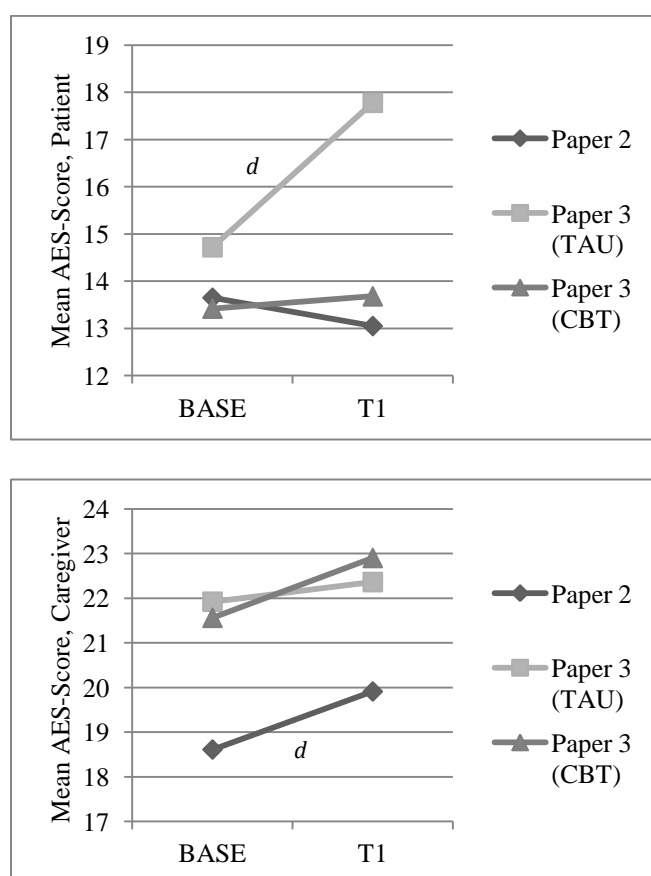
There is, however, a need for further clarification regarding domain specific aspects of rating discrepancies. Investigation of the domain specific underlying mechanisms associated with rating discrepancies will allow for enhanced understanding of related risk factors, and also for implementation of more specific intervention strategies.

To sum up, the results of Paper 1 indicate that rating discrepancies of apathy, depression, ADL, and QoL are unique. Further, when comparing rating discrepancies of different domains, various factors such as characteristics of the construct and the sample, the assessment methods, the items and the severity of the symptoms should be taken into consideration.

### **4.3 The Longitudinal Course of Rating Discrepancy in Apathy**

The present thesis has contributed to research on the longitudinal development of rating discrepancy in mild AD in several ways. Paper 2 examined longitudinally patient-caregiver rating discrepancies of apathy distinguishing between positive and negative rating discrepancies. Whereas the participants in Paper 2 underwent no intervention, the participants

in Paper 3 either received a treatment as usual or a cognitive-behavioural treatment. Furthermore, Paper 3 showed the association between baseline rating discrepancy in apathy and the therapeutic process variables over the different modules. In Figure 2 the patient and caregiver scores of the Apathy Evaluation Scale (AES) at baseline (BASE) and at follow-up (T1) of Paper 2 and 3 are depicted graphically.



*Note:  $d$  = Cohen's  $d$ . AES rating of the patients showed in Paper 3 a moderate treatment effect ( $d = 0.61$ ) and AES rating of the caregivers in Paper 2 a marginally moderate effect of time ( $d = 0.44$ ). All other effect sizes were low. TAU = treatment as usual; CBT = cognitive-behavioural treatment.*

Figure 2. Patient and caregiver scores of the Apathy Evaluation Scale (AES) at baseline (BASE) and at follow-up (T1) of Paper 2 and 3.

Papers 2 and 3 showed inconsistent findings regarding the temporal course of the rating discrepancy in apathy. In Paper 2 rating discrepancy increased and in Paper 3 it remained constant in the CBT group and it decreased in the TAU group within one year. Consideration of patient and caregiver ratings separately in exploring the longitudinal course of rating

discrepancies illustrates that in Paper 2 patient apathy ratings remained stable and caregiver apathy ratings showed a significant increase from baseline to follow-up. In Paper 3, patients' and caregivers' ratings remained stable in the CBT group. While in the TAU group the patients' apathy ratings increased and the caregiver ratings did not change.

Patients' apathy ratings in Paper 2 and Paper 3 appear comparable, but caregivers in Paper 3 rated apathy potentially higher than caregivers in Paper 2, which could be due to caregiver burden. An independent *t*-test showed significant differences in caregiver burden ( $t = 4.848, p = .000$ ) and no differences in the cognitive state (Mini-Mental State Examination (MMSE)) ( $t = -.88, p = .380$ ) between Paper 2 and Paper 3. Therefore, the divergence of the findings might not be explained by the cognitive state, but rather by the caregiver rating bias. This is in line with Conde-Sala et al. (2014), who reported that the cognitive status has a minimal influence on the rating discrepancies in QoL over time. Conversely they also reported an association between caregiver burden at baseline and change in QoL-caregiver ratings. Hence, it is possible that caregivers with a certain extent of burden are unable to perceive changes in the behavior of the patients, which could explain the stability of the caregiver apathy ratings in Paper 3.

In addition, Paper 3 suggested that the greater the rating discrepancy, the more negatively the patient assessed the therapeutic alliance. Since the therapeutic alliance is considered to be an important aspect of successful treatment and has been found to be a consistent predictor of therapy outcomes in a variety of mental disorders (Castonguay, Constantino, & Grosse Holtforth, 2006), rating discrepancy (or contained aspects such as impaired awareness of deficits) could possibly lead to a worse intervention outcome via lower therapeutic alliance. The findings indicate that the therapist should consciously deal with aspects of the relationship and should invest more effort in establishing a therapeutic alliance when treating patients with impaired awareness.

Consideration of the findings of the longitudinal analyses and the multifactoriality of rating discrepancies, indicates that patient and caregiver ratings should be analysed separately in exploring the longitudinal course of rating discrepancies. Further inputs for longitudinal studies concerning rating discrepancy in apathy are given in the next section.

#### **4.4 Implications for Research and Clinical Practice**

Several implications for further research are already given previously in the discussion section. In the following, three major issues, which should be addressed in the future research and have implication for clinical practice, are pointed out: first, the examination of the relationship between the factors of rating discrepancy; second, new approaches for investigating the longitudinal course; and third, the evaluation of the relationship between psychosocial interventions and rating discrepancies.

##### **4.4.1 The Relationship among the Factors of Rating Discrepancy in Apathy**

It remains unresolved how much caregiver burden, impaired awareness of deficits, and the severity of the apathy symptoms contribute to the rating discrepancy in apathy in mild AD. There are associations between the three main predictors of rating discrepancy, which could lead to confounding results. Impaired awareness of deficits predicts apathy (Starkstein et al., 2010) and caregiver burden (Turró-Garriga et al., 2013) and additionally, apathy and caregiver burden are related too (Rocca et al., 2010). According to the present thesis the impact of the cognitive state seems to be relatively low and negligible. Future studies should illuminate relational or, if possible, causal associations between impaired awareness of deficits, caregiver burden, and apathy in relation to patient-caregiver discrepancy in apathy ratings.

In addition, recent findings suggest that rating discrepancies differ due to cultural and social factors, which indicates important directions for further research (Mograbi et al., 2015;

Reamy, Kim, Zarit, & Whitlatch, 2011; Stella et al., 2015). Ethical and cultural differences in caregiving are already well known and explored in various studies (Dilworth-Anderson, Williams, & Gibson, 2002) and could explain, why caregiver burden was not an individual predictor of rating discrepancy in studies with a Chinese and a Singaporean sample (Huang et al., 2009; Tay et al., 2014). Little is known about cross-cultural differences in impaired awareness of deficits (Mograbi et al., 2012, 2015). Further studies might investigate whether cultural, ethical, or social differences in rating discrepancies are based on differences in caregiver burden, impaired awareness of deficits or on other factors.

The clarification among the factors of rating discrepancy may have important clinical implications. As proxies are a valuable source, we do not have the luxury of choosing the ideal proxy in clinical practice. Therefore, one goal should be to maximize the accuracy of the caregiver ratings, since inaccurate or biased caregiver reports could influence diagnosis and therefore the type and the frequency of treatment. This can in turn have negative long-term effects on the patient's health and well-being as well as a considerable impact on healthcare. A strategy to raise accuracy could be to design items that are clear and objective and that ask about observable attributes, which refer to a direct aspect of a task (Magaziner et al., 1997). Further, raising accuracy may be achieved by knowing the potential impact of caregiver burden on caregiver ratings. Paper 1 shows that caregiver rating bias is already present in slightly burdened caregivers. As reported in the previous section, caregivers in Paper 3 rated apathy potentially higher than caregivers in Paper 2, which could be due their level of burden. In Paper 2, caregivers had a mean score (SD) of 14.89 (12.32) and in Paper 3 of 26.71 (10.92) in the Zarit Burden Interview (ZBI) (Zarit, Reever, & Bach-Peterson, 1980), and according to Braun, Scholz, Hornung, and Martin (2010) they were marginally and little burdened, respectively. Thus, there is probably a positive linear correlation between caregiver burden and the caregiver rating. Further studies could examine bias corrections in relation to the level of burden to define clinical standards about how much the caregiver rating on which level of

burden should be reduced. An alternative approach would be to declare a cut-off score of the validity of the caregiver rating. As for the ZBI a cut-off score of 26 has been proposed (Schreiner, Morimoto, Arai, & Zarit, 2006), this could also be a cut-off score of the validity of the caregiver rating. This assumption should also be examined in further studies.

Guidelines that give information about how to combine the ratings from patients and caregivers would be beneficial for the application of the Apathy Evaluation Scale (AES) (Marin, Biedrzycki, & Firinciogullari, 1991), in which the clinician includes clinical observations and self- and informer reports for their ratings of the apathy symptoms. For the AES, it is not defined how to weight the caregiver ratings and how to combine the different sources (except some items that are based directly on patients' self-reports). The applicability and the psychometric quality of the AES, therefore, could be raised by the declaration of a cut-off score of the bias or a bias correction.

Additional information about the relationship of the components of rating discrepancy would also be beneficial for adapting the strategy of using rating discrepancy as a measure of impaired awareness of deficits and for raising reliability and validity. According to the present thesis, five points should be taken into account when measuring impaired awareness by rating discrepancies:

1. Considering caregiver burden because of the caregiver rating bias.
2. Considering the level of the symptoms. To some extent possible by dividing the discrepancy score by the mean of the patient and caregiver (Clare, Nelis, Whitaker, et al., 2012).
3. Neglecting positive rating discrepancies because they seem to contain other underlying processes than impaired awareness.
4. Considering domain specificity, as different domains underlie different processes.
5. Integrating a clinician rating for method variance.

Finally, the present thesis provides the impulse for a change in perspective that it may be more important to use the ratings of patient and caregivers as complementary and not as composite scores. Clinicians should be suspicious, when large negative rating discrepancies (greater caregiver than patient reported deficits) are noted, since they could implicate issues on the side of the patient, the caregiver, or on the relationship. Further, the possibility of a development of apathy and appropriate interventions should be considered.

#### **4.4.2 Investigating Rating Discrepancy in Apathy over Time**

According to the findings of the present thesis, rating discrepancy represents dynamic processes of the patient-caregiver dyad. As shown in Paper 3, the convergence of the caregiver and the patient ratings do not necessarily reflect beneficial processes. Furthermore, a recently presented explanation for different developments of patient and caregiver ratings over time might be due to temporally shifted, non-parallel perceptions of changes in relation to different adaption processes of the patient and the caregiver (Conde-Sala et al., 2014). This dynamic should be investigated in further longitudinal studies with statistical methods considering within couple dependencies (Kenny, Kashy, & Cook, 2006). Ideally the variables of interest are assessed at multiple occasions over a short period of time with short time intervals, to gain more insight into possible indicators for contextual aspects suggesting different interpretations of the ratings and their functions. An outcome variable, which was considered as stable over time, might be a result of a dynamic-adaptive and context-dependent process of the manifested variables (Boker & Martin, 2013).

Paper-and-pencil questionnaires and face-to-face clinical interviews are limited in a number of ways, including their reliance on patients' and informants' retrospective reports, the skill of the clinical interviewer, and the artificial setting of the assessment (Trull & Ebner-Priemer, 2013). The 'experiencing self' is functionally and neuroanatomically different from the 'remembering' and 'believing' selves measured through retrospective and trait



questionnaires (Trull & Ebner-Priemer, 2013). To date, just a few attempts have been made to study apathetic patients with AD in their natural environment using ambulatory assessment methods (König et al., 2014). Moreover, literature suggests that individual and environmental factors play a crucial role in nonpharmacological interventions for apathy (Brodaty & Burns, 2012). Therefore, I suppose that momentary self- and informer report techniques, such as ambulatory assessments, which allow patients and caregivers to report experiences that are happening in real time across multiple moments in their daily lives, would be beneficial for apathy assessment.

Conducting longitudinal studies using ambulatory patient and caregiver reports, which might be based on information and communication technologies devices, might provide a better understanding of the factors of rating discrepancy and the dynamic processes of the dyad.

#### **4.4.3 Interventions Targeting Factors of Rating Discrepancy in Apathy**

Further research is required to explore the relationship between impaired awareness of deficits and psychosocial interventions in AD in more detail, with a particular focus on the characteristics of the caregiver and the dyadic situation. Based on the biopsychosocial model (Ownsworth et al., 2006), patients with impaired awareness may benefit most from individualized psychosocial treatments with a focus on the psychological factors (e.g. denial and coping style) or on the social factors (e.g. stigma, exclusion, and social desirability). Since the present thesis indicates domain specificity, it is of great importance to evaluate in further studies different kinds of interventions in relation to impaired awareness of different domains.

The findings of Paper 3 suggested that impaired awareness could possibly lead to a worse intervention outcome via lower therapeutic alliance. Hence, patients with an increase in awareness in the course of the therapy might profit especially from an intervention targeting

neuropsychiatric symptoms. Future longitudinal studies should investigate the development of impaired awareness of deficits and the change of patients' perception of the therapeutic process in the course of the treatment to clarify the relationship between the therapeutic process and impaired awareness. Furthermore, including the therapists' perspective of the therapeutic process could potentially provide more insight into the treatment of patients with impaired awareness of deficits. In general, the effectiveness of a treatment might be raised when considering the level of awareness and adapting the therapeutic work to the special needs of patients with more impaired awareness, for instance by reinforcing therapeutic alliance, clarifying motivational aspects, using more individualized techniques, and counselling caregivers.

But, there is also a need to find ways of improving caregivers' perceptions of the patient's status so as to help reduce the burden they experience, since stress in the caregiver can also impact negatively on the patient (Conde-Sala et al., 2014). Moreover, the caregiver rating bias can lead to substantial distortions, which might influence diagnosis and therefore, the type and frequency of treatment. Psychoeducational and therapeutic interventions may be one way of enabling caregivers to learn more about dementia and neuropsychiatric symptoms, to improve their relationship with the patient, and to help them cope with the stress that is an inherent part of caring for someone with AD (Conde-Sala et al., 2014). Due to the demands of caregiving many of the face-to-face programs are inaccessible to caregivers and intervention programs that are too effortful could produce additional burden and are therefore contraindicated (Hu, Kung, Rummans, Clark, & Lapid, 2015; Prick, de Lange, Twisk, & Pot, 2015). Hence, technology-based interventions utilizing telephones, mobile phones, videophones, computers, and the internet might be beneficial for burdened caregivers because they are accessible 24 hours a day and 7 days a week. A recent review showed that internet-based interventions for caregivers are effective in reducing aspects of caregiver stress and improving their well-being (Hu et al., 2015). With continued acceptance of internet use in

elderly people, there are additional opportunities to use this platform to improve the caregivers' lives (Hu et al., 2015).

Under the aspect of multifactoriality of rating discrepancies, treatments including both the patient and the caregiver might be advantageous. According to Paper 3, the therapist should consider that in the setting couples counselling, patients might feel more offended and could perceive less therapeutic bond because there are two counterparts, the caregiver and the therapist, who might build an alliance. Moreover, home-based psychosocial interventions for patients and caregivers could be an effective approach to improve patients' awareness of deficits, to reduce caregiver burden and to increase caregivers' understanding and handling of neuropsychiatric symptoms. In addition, it might have a beneficial effect on the relationship between patient and caregiver (George & Padmam, 2014; Prick et al., 2015).

## **4.5 Final Conclusions**

The present thesis provides a significant contribution to the current understanding of apathy rating discrepancy in mild AD. First, the findings indicate multifactoriality and domain specificity of rating discrepancies. Second, the findings pave the way for future longitudinal studies of rating discrepancy in apathy and research in relation to psychosocial treatments. Third, the present thesis provides insight about the following different functions of rating discrepancies in apathy: as an indicator of caregiver burden and the potential of a caregiver rating bias, as a measure of awareness of deficits, as a reflection of dyadic processes, as a risk factor for a clinical apathy, and as an indicator of differential effects of psychosocial interventions. Finally, the thesis suggests that a large rating discrepancy does not necessarily indicate that information from the patient or the caregiver is invalid, but rather that it may have additional value and should be regarded as useful clinical information.

## 5 PUBLICATIONS

### **5.1 Paper 1: ‘Caregiver rating bias in mild cognitive impairment and mild Alzheimer’s disease: Impact of caregiver burden and depression on dyadic rating discrepancy across domains’**

(Livia Pfeifer, Reinhard Drobetz, Sonja Fankhauser, Moyra E. Mortby, Andreas Maercker, Simon Forstmeier)

#### **5.1.1 Abstract**

**Background:** Caregivers of individuals with dementia are biased in their rating of mental health measures of the care receiver. This study examines caregiver burden and depression as predictors of this bias for mild cognitive impairment and mild Alzheimer’s disease in different domains.

**Methods:** The sample consisted of 202 persons: 60 with mild cognitive impairment, 41 with mild Alzheimer’s disease, and 101 caregivers. Discrepancy scores were calculated by subtracting the mean caregiver score from the respective mean patient score on the following assessment instruments: the Geriatric Depression Scale (GDS), Apathy Evaluation Scale (AES), Bayer-Activities of Daily Living scale (B-ADL), and Quality of Life-AD scale (QoL-AD). Caregiver burden and depression were assessed by the Zarit Burden Interview (ZBI) and the Center for Epidemiologic Studies Depression scale (CES-D).

**Results:** Intraclass correlation coefficients (ICC) were low for apathy (.38), daily functioning (.38), and quality of life (.30) and moderate for depression (.49). These showed negative rating discrepancies, which indicates caregiver rating bias for all four domains. Regression analyses revealed that caregiver burden significantly contributed to explaining these discrepancies in the domains apathy, daily functioning, and quality of life.

Conclusion: Caregiver rating bias can be attributed to caregiver burden. When caregiver burden is present, data, based on caregiver ratings should therefore be interpreted with caution.

### **5.1.2 Introduction**

Significant differences between the rating of mental health measures by individuals with dementia and the reports of their caregivers are well documented (Farias et al., 2005; Leicht et al., 2010; Schulz et al., 2013). Discrepancy scores are often interpreted as a standard measure of how accurately patients with Alzheimer's disease (AD) are aware of cognitive impairment and deficits. The more the caregiver's rating exceeds the patient's rating, the more diminished is the patient's awareness (Clare, 2004). However, analyzing possible caregiver predictors of discrepancy scores leads to the assumption that dyadic rating discrepancy is associated not solely with patients' reduced awareness, but also with caregiver characteristics. Hence, dyadic rating discrepancy might reflect a combination of patients' underrating their own suffering and caregivers' overestimating the patient's suffering - the caregiver rating bias. Several studies were indeed able to provide evidence for such a bias in various domains, but they show inconsistent findings regarding factors that contribute to it (Chang et al., 2011; Clare, Nelis, Martyr, Roberts, et al., 2012; Conde-Sala et al., 2009; Ready et al., 2004; Sands et al., 2004; Schulz et al., 2013). Discrepancies in reporting depressive symptoms have been found in several studies. Rosenberg et al. (2005) and Teri and Truax (1994) showed that caregiver burden and depression contribute to caregiver ratings of patients' depressive symptoms. Caregiver burden alone was found to be the only significant predictor of discrepancies in rating depression in Chang et al. (2011) and Burke et al. (1998), but neither study addressed the influence of caregiver depression. Similar results were reported in studies on dyadic rating discrepancies in rating activities of daily living (ADL). Some researchers reported caregiver burden to be associated with the discrepancy scores (Clare, Nelis, Martyr, Roberts, et al.,

2012; Long Schatzberg, Sudha, & Mutran, 1998; Zanetti, Geroldi, Frisoni, Bianchetti, & Trabucchi, 1999), although only Zanetti et al. (1999) assessed both caregiver burden and depression. In contrast, Argüelles et al. (2001) showed that caregiver depression but not burden was related to caregiver rating bias. For quality of life, the domain with the most numerous and most current studies, the consensus was that caregiver burden is a strong predictor of dyadic rating discrepancy (Conde-Sala et al., 2009; Karlawish et al., 2001; Sands et al., 2004; Schulz et al., 2013). Caregiver depression, however, was seen as tending to play a less significant role in the dyadic rating discrepancy of quality of life (Karlawish et al., 2001; Schulz et al., 2013).

To our knowledge, no study until now has evaluated caregiver burden or depression as predictors of dyadic rating discrepancy in apathy. Apathy, defined as a lack of motivation, i.e. behavioral, cognitive, and emotional concomitants of goal-directed behavior, is one of the most prevalent neuropsychiatric symptoms in AD and mild cognitive impairment (MCI) (Clarke et al., 2011). Although definitions of apathy and depression overlap in terms of key symptoms, apathy may be viewed as distinguishable from depression in dementia (Mortby et al., 2012). Apathy measurements are usually based on self- and informant reports. Because apathy is associated with caregiver burden, investigating the influence of caregiver burden on caregivers' apathy ratings is of major importance. Accurate assessment is crucial to improving understanding and management of apathy (Clarke et al., 2011).

However, caregiver burden and depression are the most widely used caregiver variables for explaining dyadic rating discrepancy and appear to contribute to the caregiver rating bias in various domains. Care of cognitively impaired people is physically and mentally demanding and often associated with burden and depression. In addition, caregiving may lead to a distorted perception and exaggeration of the patient's symptoms (Schulz et al., 2013). Caregiver burden and depression can be considered as two separate variables. Caregiver

burden is defined as a reaction to the physical, emotional, economic, and social costs of the caregiving relationship, while caregiver depression is a mood disturbance triggered by the stress of providing care and manifested as feelings of loneliness, isolation, fearfulness, and being easily annoyed (Pinquart & Sörensen, 2003). Behavioral problems, limited ADL, and cognitive impairment are strongly related to caregiver burden and depression (Pinquart & Sörensen, 2003; Schoenmakers, Buntinx, & Delepeleire, 2010). In addition, caregiver depression seems to be mediated by caregiver burden (Clyburn, Stones, Hadjistavropoulos, & Tuokko, 2000).

It remains unresolved, however, whether caregiver burden or depression predicts caregiver rating bias within specific domains in a similar way, or if there are domain-specific differences. Clare, Nelis, Martyr, Roberts, et al. (2012) alone demonstrated a domain unspecificity in predictors of rating discrepancies in the domains of memory, ADL, and social functioning. Caregiver burden was associated with discrepancies in rating memory and ADL but not social functioning; caregiver depression was not addressed. On the basis of the results presented above, one might assume that caregiver burden is a factor that predicts rating discrepancies in various domains. But even if the study samples are similar (patients with mild to moderate dementia), the results are based on different methods and hence only comparable to a limited extent. To our knowledge, no study has analyzed the association between both caregiver burden and depression and caregiver rating bias simultaneously across various domains such as depression, apathy, daily functioning, and quality of life. These domains are of high relevance for dementia and are often assessed by informant reports.

Hence, the main purpose of the current study was to examine domain-specific relationships between caregiver burden or depression and dyadic rating discrepancies. We hypothesized that caregiver burden is a more prominent predictor than caregiver depression of dyadic rating discrepancy. We also hypothesized the association between caregiver burden or

caregiver depression and the dyadic rating discrepancy to be domain-specific. Furthermore, we explored the extent to which discrepancies were related to severity of cognitive impairment and to patient-caregiver relationship, as it is not yet clear to what degree these variables influence the rating discrepancy (Farias et al., 2005; Mougias, Politis, Lyketsos, & Mavreas, 2011).

### **5.1.3 Methods**

#### **Participants**

Participants were 101 elderly individuals, 60 of them with MCI and 41 with AD (see Table 3). The sample was derived from the Swiss longitudinal study "Motivational Reserve as a Protective Factor in Mild Alzheimer's Dementia and Mild Cognitive Impairment" (MoReA); only baseline data were used. Participants were recruited from 17 collaborating local hospitals or clinics in the German-speaking part of Switzerland. For inclusion, subjects had to be diagnosed with either MCI or mild AD and had to be age 60 or older.

In each of the cooperating memory clinics, an interdisciplinary team assigned the diagnosis after thorough neurological, psychiatric, clinical and neuropsychological assessments. Clinical dementia was diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 2000). To meet a diagnosis of AD, gradual onset and progressive deterioration of cognitive functioning and the exclusion of all other specific causes of dementia were necessary. Our clinical diagnosis of AD corresponds to the diagnosis of "probable Alzheimer's disease" according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). Only mild AD cases with a score of 1 on the Clinical Dementia Rating scale (CDR) (Morris, 1997) and scores between 18 and 26 on the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) were included. The MCI



diagnosis was based on international consensus criteria (Winblad et al., 2004), including the following criteria: absence of dementia as diagnosed by DSM–IV criteria (MMSE  $\geq$  24); cognitive decline, i.e. self- and/or informant report and impairment in completing objective tasks, and/or evidence of decline over time on objective cognitive tasks; preserved basic ADL and not exceeding minimal impairment in complex instrumental functions (CDR  $\leq$  0.5); at least mild impairment in one of the following cognitive domains: memory, language, praxis, executive function, or attention. Exclusion criteria of the present study were a history of a malignant disease, severe organ failure, metabolic or hematologic disorders, neurosurgery or neurological condition such as Parkinson's disease, epilepsy, and postencephalitic and postconcussional syndrome.

Each participant was required to be accompanied by a reliable collateral source, typically the partner; a child or a close friend was also accepted. Although level of impairment of the patients in the present study was relatively low, it can be assumed that the family members and friends performed a caregiving function (Garand, Amanda Dew, Eazor, DeKosky, & Reynolds, 2005). Written informed consent was obtained prior to inclusion from all participants and caregivers.

General cognitive functioning of the patients was assessed with the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). For the assessment of neuropsychiatric symptoms the Neuropsychiatric Inventory (NPI) (Jeffrey L Cummings, 1997) a reliable, informant-based rating scale was used. Severity and frequency of 12 neuropsychiatric symptoms that are typical of dementia are scored on the basis of structured questions. Scores range from 0 to 144, with higher scores indicating more severe symptoms.

## **Measures**

The following assessment instruments for the patient's abilities or difficulties were administered with parallel forms to patient and caregiver separately. Depression was

measured with the Geriatric Depression Scale (GDS) (Yesavage et al., 1986), a frequently used instrument for screening depression in the elderly. The short version consists of a series of 15 yes/no self-referent statements to identify the presence of depression. The Apathy Evaluation Scale (AES) (Marin et al., 1991) was developed for multiple rater sources (clinician, informant and self) to quantify and characterize apathy in adult patients. The scale comprises 18 items, which are rated on a 4-point scale with the following categories: not at all characteristic, slightly characteristic, somewhat characteristic, and very characteristic. We assessed daily functioning by the Bayer-Activities of Daily Living Scale (B-ADL) (Erzigkeit et al., 2001). The scale was developed within an international research project to assess deficits in performance of everyday activities in patients with mild to moderate dementia. The B-ADL scale consists of 25 items concerning frequency of difficulties, with a 10-point response scale ranging from “never” to “always”. The Quality of Life-AD (QoL-AD) (Logsdon, Gibbons, McCurry, & Teri, 1999) is based on direct interviews with AD patients and a questionnaire, consisting of 13 items on a 4-point scale. Responses are rated from 1 (poor) to 4 (excellent).

Caregivers completed the following measures on their own account. The Zarit Burden Interview (ZBI) (Zarit et al., 1980), a 22-item self-report inventory of perceived caregiver strain. Guidelines suggest interpreting severity of burden as follows: 61-88 as severe, 41-60 as moderate, 21-40 as weak and scores under 21 as hardly at all (Braun et al., 2010). To assess depression in caregivers we used the short form of the Allgemeine Depressionsskale (ADS-K) (Hautzinger & Bailer, 1993), the German version of the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). The critical cut-off point for this 15-item scale is a summary score of 18.

## Data Analysis

All statistical analyses were performed at an alpha level of 0.05 (two-tailed), using IBM SPSS Statistics 20.0. Descriptive statistics included frequencies for categorical variables (gender and relationship) and means and standard deviations (SD) for continuous measures (age patient, age caregiver, years of education, MMSE, neuropsychiatric symptoms, caregiver burden, and years of relationship) for the entire sample as well as for the MCI and the AD group separately. Chi-square analyses were used to assess associations between categorical variables, and independent t-tests to compare continuous measures between groups.

The level of agreement between patients' and their caregivers' ratings was determined using intraclass correlation coefficients (ICC). ICC <0.40 indicated weak agreement, 0.40-0.75 represented moderate to good agreement, and ICC >0.75 indicated outstanding agreement (Lee, Koh, & Ong, 1989). Paired t-tests were run to determine whether patient- and caregiver ratings differed significantly. Effect sizes were calculated using Cohen's  $d$ :  $d = 0.2$  was taken to indicate a small,  $d = 0.5$  a moderate, and  $d = 0.8$  a large effect size (Cohen, 1988).

Raw discrepancy scores for depression, apathy, daily functioning, and quality of life were calculated by subtracting the mean caregiver score from respective mean patient score. Reversing the polarity of the QoL-AD scores made the values more comparable of those of the other scales, i.e. a higher score indicated a poorer status. Discrepancy scores differing significantly from zero provide evidence for a systematic bias; this was proved with a dependent t-test. A mean score difference lower than zero indicates that either status of the patients was underestimated by themselves or overestimated by the caregivers.

To explore the relationship between all variables, bivariate correlations were calculated. Furthermore, domain-specific stepwise multiple regression equations were conducted to determine the extent to which caregiver burden and depression were associated with the

occurrence of rating discrepancies. Potential multicollinearities of the independent variables were evaluated. Because our sample size was relatively small, only a small number of variables could be considered. On the basis of the literature, we entered in the first step patients' age, sex, education, and neuropsychiatric symptoms in the model as control variables. By integrating the diagnosis (MCI/AD) in the second step, effects caused by the cognitive state could be controlled. For the same reason, in a third step the type of relationship (spouse versus others) was entered into the model. The final variables entered were caregiver burden and depression.

#### **5.1.4 Results**

Patient and caregiver characteristics are presented in Table 3. The overall study group was comprised of 60 patients with MCI and 41 with AD. The two groups differed significantly in patients' age, gender, and cognitive status (MMSE), as well as in caregiver burden, the relationship, and their living arrangements. Only 14.6% of the AD patients lived in nursing homes. MCI patients were younger than the AD patients ( $t(99) = -3.79, p < .001$ ) and had higher MMSE scores ( $t(60) = 7.80, p < .001$ ). A lower percentage of the MCI patients were female ( $\chi^2(1) = 6.51, p < .05$ ). Furthermore, the MCI caregivers were less burdened than the AD caregivers ( $t(99) = -2.54, p < .05$ ) and more often spouses ( $\chi^2(4) = 11.33, p < .05$ ). Group differences in caregivers' age were explained by the varying types of relationship between patients and caregivers. Of the MCI patients, 71.7% were accompanied by spouses, in contrast to only 46.3% of the, AD patients, who were more often accompanied by other family members, such as their children. In the present study, caregivers were marginally burdened and depressed.

Table 3 Characteristics of study participants and group comparisons

|                               | Total         | MCI           | AD            | $t/\chi^2$ | p    |
|-------------------------------|---------------|---------------|---------------|------------|------|
| <u>Patients <i>N</i></u>      | 101           | 60            | 41            |            |      |
| Age, mean                     | 77.22 (8.19)  | 74.82 (7.51)  | 80.73 (7.95)  | -3.79      | .000 |
| Education, years              | 13.18 (10.89) | 14.15 (13.64) | 11.62 (3.02)  | 1.37       | .175 |
| Gender (% female)             | 50.5          | 40            | 65.9          | 6.51       | .011 |
| MMSE                          | 25.26 (3.27)  | 26.98 (2.04)  | 22.64 (3.06)  | 7.80       | .000 |
| NPI                           | 7.4 (11.03)   | 6.68 (9.92)   | 8.44 (12.53)  | -.75       | .455 |
| <u>Caregivers <i>N</i></u>    | 101           | 60            | 41            |            |      |
| Age, mean                     | 65.90 (13.30) | 67.25 (13.47) | 63.95 (12.97) | 1.23       | .221 |
| Gender (% female)             | 75.2          | 76.7          | 73.2          | 0.16       | .689 |
| Burden (ZBI)                  | 15.24 (12.62) | 12.67 (12.34) | 19.01 (12.21) | -2.54      | .013 |
| Depression (CES-D)            | 6.24 (6.29)   | 6.01 (6.47)   | 6.59 (6.09)   | -0.46      | .650 |
| Relationship <i>N</i> (%)     |               |               |               | 11.33      | .023 |
| Partner                       | 61.4          | 71.7          | 46.3          |            |      |
| Child                         | 25.7          | 18.3          | 36.6          | 18.3       |      |
| Other                         | 12.9          | 10.0          | 17.1          | 10.0       |      |
| Relationship, years           | 47.10 (14.79) | 44.86 (15.67) | 50.38 (12.90) | -1.89      | .062 |
| Living situation <i>N</i> (%) |               |               |               | 15.85      | .003 |
| Alone                         | 26.7          | 25.0          | 29.3          |            |      |
| Partner                       | 60.4          | 71.7          | 43.9          |            |      |
| Other                         | 5.0           | 1.7           | 9.8           |            |      |
| Nursing Home                  | 5.9           | 0             | 14.6          |            |      |

*Note.*  $t$ ,  $\chi^2$ : values of statistics from the paired t-tests (with standard deviation) and chi-square tests; NPI = Neuropsychiatric Inventory, ZBI = Zarit Burden Inventory, CES-D = Center for Epidemiologic Studies Depression Scale, Relationship, years: Years of knowing each other.

To assess the dyadic rating agreement, we calculated ICCs (s. Table 4). ICCs of apathy (.38), daily functioning (.38), and quality of life (.30) were low, and those of depression moderate (.49). Patient and caregiver ratings differed significantly in all four domains (GDS:  $t(100) = -3.26$ ,  $p < 0.01$ ; AES:  $t(100) = -5.86$ ,  $p < 0.000$ ; B-ADL:  $t(100) < -4.29$ ,  $p < 0.000$ ;

QoL-AD:  $t(100) = -4.58, p < 0.000$ ). All discrepancy scores showed a negative value, differing significantly from zero. The statistical magnitude of this bias, defined by the effect size  $d$ , was low for depression and moderate for apathy, daily functioning, and quality of life.

Table 4 Dyadic discrepancy in depression, apathy, daily functioning, and quality of life

| Scale | Patient Self-Rating | Caregiver Rating of the Patient | Discrepancy    | $t$      | Cohens $d$ | ICC |
|-------|---------------------|---------------------------------|----------------|----------|------------|-----|
| GDS   | 3.37 (2.65)         | 4.39 (3.52)                     | -1.03 (3.16)   | -3.26**  | 0.33       | .49 |
| AES   | 13.93 (6.61)        | 19.97 (11.36)                   | -6.04 (10.37)  | -5.86*** | 0.65       | .38 |
| ADL   | 69.14 (37.52)       | 92.86 (57.73)                   | -23.35 (54.42) | -4.29*** | 0.49       | .38 |
| QOL   | -39.69 (5.00)       | -36.76 (5.82)                   | -2.93 (6.44)   | -4.58*** | 0.54       | .30 |

*Note.*  $N=101$ ; GDS = Geriatric Depression Scale, AES = Apathy Evaluation Scale, B-ADL = Bayer-Activities of Daily Living Scale, QOL = Quality of Life-AD; ratings and discrepancy: mean with standard deviation;  $t$ : value of t-statistic from the paired t-test, \*\* $p < .01$ , \*\*\* $p < .001$ ; ICC: intraclass correlation coefficient.

Bivariate correlations among discrepancy scores are shown in Table 5. All discrepancy scores were significantly positively related to each other and negatively to caregiver burden. In addition, depression-rating discrepancy was related to patient's age and to caregiver depression. Apathy-rating discrepancy was associated with the patient's neuropsychiatric symptoms. Rating discrepancy of daily functioning was related to patient's age and gender, MMSE, caregiver's age, and the relationship. Rating discrepancy of quality of life was related to the duration of the patient-caregiver relationship. The correlation coefficient between caregiver burden and depression was .50 ( $p < .01$ ).

Table 6 displays results of the multivariate linear regression analyses. Caregiver burden significantly contributed to explaining dyadic rating discrepancies in apathy, daily functioning, and quality of life. Depression discrepancy was predicted by caregiver burden

and depression with a similar non-significant  $\beta$  value. However, we observed a significant change in  $R^2$  in step four of the depression discrepancy. The type of relationship (spouses vs. others) did not predict any dyadic rating discrepancy. Only discrepancies in rating daily functioning were predicted by diagnosis; these were smaller for patients with MCI than with AD. Moreover, patient's age was a significant predictor for rating discrepancies in depression and daily functioning. These results reflect the unique contribution of caregiver burden in predictions for each domain, over and above the effects of covariates.

Table 5 Bivariate correlations among study variables

|                       | 1       | 2       | 3    | 4     | 5      | 6      | 7    | 8     | 9     | 10      | 11    | 12     | 13     | 14    | 15 |
|-----------------------|---------|---------|------|-------|--------|--------|------|-------|-------|---------|-------|--------|--------|-------|----|
| <u>Patient</u>        |         |         |      |       |        |        |      |       |       |         |       |        |        |       |    |
| 1. Age                | 1       |         |      |       |        |        |      |       |       |         |       |        |        |       |    |
| 2. Gender (1=m; 2=f)  | .05     | 1       |      |       |        |        |      |       |       |         |       |        |        |       |    |
| 3. Education (years)  | -.04    | -.21*   | 1    |       |        |        |      |       |       |         |       |        |        |       |    |
| 4. NPI                | -.11    | -.06    | -.03 | 1     |        |        |      |       |       |         |       |        |        |       |    |
| 5. MMSE               | -.43*** | -.14    | .07  | .10   | 1      |        |      |       |       |         |       |        |        |       |    |
| <u>Caregiver</u>      |         |         |      |       |        |        |      |       |       |         |       |        |        |       |    |
| 6. Age                | .13     | -.21*   | .02  | -.03  | .09    | 1      |      |       |       |         |       |        |        |       |    |
| 7. Gender (1=m; 2=f)  | .31**   | -.52*** | .11  | -.05  | -.06   | -.11   | 1    |       |       |         |       |        |        |       |    |
| 8. Relationship       | -.29**  | -.54**  | .12  | .10   | .20*   | .59*** | -.13 | 1     |       |         |       |        |        |       |    |
| 9. Relationship years | .44***  | .21*    | -.06 | -.04  | -.11   | .37*** | -.01 | -.13  | 1     |         |       |        |        |       |    |
| 10. Burden            | .14     | -.05    | -.00 | .15   | -.33** | -.00   | .06  | -.12  | .03   | 1       |       |        |        |       |    |
| 11. Depression        | .03     | -.16    | .10  | .02   | -.18   | .13    | -.03 | .04   | .10   | .50***  | 1     |        |        |       |    |
| <u>Discrepancy</u>    |         |         |      |       |        |        |      |       |       |         |       |        |        |       |    |
| 12. GDS               | -.22*   | -.08    | .04  | -.17  | .04    | -.12   | -.01 | .00   | -.19  | -.31**  | -.25* | 1      |        |       |    |
| 13. AES               | -.10    | .04     | .17  | -.20* | .06    | -.13   | .04  | -.03  | -.12  | -.37*** | -.18  | .32**  | 1      |       |    |
| 14. ADL               | -.37*** | -.21*   | .05  | -.08  | .40*** | .20*   | -.05 | .32** | -.08  | -.39*** | -.14  | .39*** | .36*** | 1     |    |
| 15. QOL               | -.01    | .06     | .10  | .17   | .02    | -.04   | .04  | .02   | -.21* | -.40*** | -.20  | .39*** | .43*** | .28** | 1  |

*Note.* The values represent Pearson correlations (between two continuous variables), point-biserial correlations (between a continuous and a dichotomous variable), or phi coefficients (between two dichotomous variables). Relationship = spouses vs. others, GDS = Geriatric Depression Scale, AES = Apathy Evaluation Scale, B-ADL = Bayer-Activities of Daily Living Scale, QOL = Quality of Life-AD; \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ .



Table 6 Results of stepwise regression analyses predicting dyadic rating discrepancies in depression, apathy, daily functioning, and quality of life

|                     | <u>GDS-Discrepancy</u> |             |         |              | <u>AES-Discrepancy</u> |             |         |              | <u>ADL-Discrepancy</u> |             |         |              | <u>QOL-Discrepancy</u> |             |         |              |
|---------------------|------------------------|-------------|---------|--------------|------------------------|-------------|---------|--------------|------------------------|-------------|---------|--------------|------------------------|-------------|---------|--------------|
|                     | <i>B</i>               | <i>SE B</i> | $\beta$ | $\Delta R^2$ | <i>B</i>               | <i>SE B</i> | $\beta$ | $\Delta R^2$ | <i>B</i>               | <i>SE B</i> | $\beta$ | $\Delta R^2$ | <i>B</i>               | <i>SE B</i> | $\beta$ | $\Delta R^2$ |
| Step 1 Patient      |                        |             |         | .11*         |                        |             |         | .08          |                        |             |         | .21***       |                        |             |         | .03          |
| Age                 | -.11                   | .04         | -.27**  |              | -.16                   | .13         | -.12    |              | -2.64                  | .62         | -.40*** |              | -.02                   | .08         | -.02    |              |
| Sex                 | -.59                   | .65         | -.09    |              | 1.63                   | 2.13        | .08     |              | -21.46                 | 10.22       | -.20*   |              | .66                    | 1.36        | .05     |              |
| Education           | .00                    | .03         | .00     |              | .17                    | .10         | .17     |              | -.03                   | .47         | -.01    |              | .07                    | .06         | .12     |              |
| NPI                 | -.06                   | .03         | -.20    |              | -.19                   | .10         | -.19    |              | -.65                   | .47         | -.13    |              | -.08                   | .06         | -.13    |              |
| Step 2 Diagnosis    |                        |             |         | .01          |                        |             |         | .00          |                        |             |         | .16***       |                        |             |         | .00          |
| MCI vs. AD          | -.68                   | .72         | -.10    |              | -.65                   | 2.39        | -.03    |              | -47.77                 | 10.25       | -.43*** |              | -.65                   | 1.52        | -.05    |              |
| Step 3 Relationship |                        |             |         | .01          |                        |             |         | .00          |                        |             |         | .02          |                        |             |         | .00          |
| Spouses vs. others  | -.87                   | .80         | -.13    |              | -1.40                  | 2.67        | -.07    |              | 18.10                  | 11.30       | .16     |              | .58                    | 1.70        | .04     |              |
| Step 4 Caregiver    |                        |             |         | .09*         |                        |             |         | .11**        |                        |             |         | .07**        |                        |             |         | .14**        |
| Burden (ZBI)        | -.04                   | .03         | -.18    |              | -.28                   | .10         | -.35**  |              | -1.14                  | .41         | -.27**  |              | -.20                   | .06         | -.39**  |              |
| Depression (CES-D)  | -.09                   | .06         | -.17    |              | -.02                   | .19         | -.01    |              | .01                    | .79         | .00     |              | .02                    | .12         | -.02    |              |

*Note.*  $N=101$ . GDS = Geriatric Depression Scale ( $R^2 = .22$ ), AES = Apathy Evaluation Scale ( $R^2 = .19$ ), ADL = Bayer-Activities of Daily Living Scale ( $R^2 = .45$ ), QOL = Quality of Life-AD ( $R^2 = .17$ ); NPI = Neuropsychiatric Inventory, ZBI = Zarit Burden Inventory, CES-D = Center for Epidemiologic Studies Depression Scale; \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ .

### 5.1.5 Discussion

The aim of the present study was to investigate to what extent caregiver burden and depression are related to caregiver rating bias regarding the patient's depression, apathy, daily functioning, and quality of life.

In accordance with previous literature, dyadic rating agreement in apathy, daily functioning, and quality of life was poor (Farias et al., 2005; Leicht et al., 2010; Ready et al., 2004; Sands et al., 2004; Schulz et al., 2013). The ICC of depression was moderate; one explanation for this divergence could be that the GDS is based on a 2-point scale, which increases the probability of agreement. Negative rating discrepancies were found in all four domains, which indicate that either the patients underrated their own suffering, or that the caregivers overestimated it, or both.

With respect to the main objective of our study, our data revealed that caregiver burden seems to be a more important predictor of caregiver rating bias than caregiver depression. Caregiver depression tended to play a less significant role in dyadic rating discrepancy. Our findings thus confirm the first hypothesis that caregiver rating bias can be attributed to caregiver burden. Consistent with our second hypothesis, our findings show domain-specific patterns. Because the predictor structure differs in relation to the domain, it is not possible to generalize the influence of caregiver burden and depression on rating discrepancies across domains. In addition, there is empirical support to show that dyadic rating discrepancy is not associated solely with reduced awareness of the patient, but also with caregiver characteristics.

The results of the regression analysis revealed a significant association between caregiver burden and rating discrepancies in apathy, daily functioning, and quality of life. Caregiver depression was not related to any rating discrepancy in these domains. These findings appear

to bolster the argument that caregiver burden and depression, albeit related, are indeed separate variables. Our findings are consistent with several studies that reported caregiver burden as being a significant predictor of rating discrepancies in daily functioning (Clare, Nelis, Martyr, Roberts, et al., 2012; Zanetti, Geroldi, et al., 1999) and quality of life (Conde-Sala et al., 2009; Mougias et al., 2011; Sands et al., 2004). Schulz et al. (2013) reported an association between caregiver burden and depression with the rating discrepancy in quality of life. Their multiple regression analysis reveals that just caregiver burden alone predicts the QoL-AD discrepancy score significantly, which is in keeping with our results. In addition, the deviance could have been caused by the sample. Caregivers in the study by Schulz et al. (2013) were indeed comparably burdened but significantly more depressed than in the present study.

To our knowledge, predictors of apathy rating discrepancy have yet to be investigated. Given that apathy is associated with caregiver burden, it is meaningful to know that caregiver burden might lead to a caregiver bias in rating apathy. In addition, the different predictor structure for apathy and depression adds to the evidence that apathy may be a distinguishable syndrome from depression in dementia (Mortby et al., 2012). Our findings regarding depression rating discrepancy, compared to the other domains, show a different pattern.  $\beta$ -values for caregiver burden and depression were similar and not significant. The results of the regression analysis may have been ambiguous, because caregiver burden and depression share a substantial portion of variance ( $r=.50$ ). However, we conducted a post-hoc analysis in which caregiver depression and burden were included separately as a single predictor in the fourth step of the multiple regression analysis. These findings confirm our assumption that both caregiver burden ( $\beta = -.27, p<.01$ ) and caregiver depression ( $\beta = -.26, p<.01$ ) predict rating discrepancy in depression. These results are also in accordance with Rosenberg et al. (2005), who concluded that caregiver depression and burden affect rating discrepancy in

depression and that a depressed informant is more likely to report depression in his or her demented proxy. Similar to our findings, the effects by Rosenberg et al. (2005) were notable but not large in magnitude, and caregivers were minimally burdened and depressed.

Our data revealed no associations between patient-caregiver relationship and rating discrepancies, which is consistent with other studies (Farias et al., 2005; Sands et al., 2004). Quality of relationship might be a better mechanism than purely the type of relationship for rating discrepancies (Farias et al., 2005). Finally, daily functioning was the only domain that was predicted by the level of cognitive impairment. The AD group showed higher discrepancy scores than the MCI group. These findings are consistent with several previous studies reporting existent or non-existent associations between cognitive impairment and rating discrepancies (Clare, Nelis, Martyr, Roberts, et al., 2012; Farias et al., 2005; Ready et al., 2004; Sands et al., 2004). Farias et al. (2005) argued that the group difference reflects a decreased awareness in patients with dementia. Our data does not support this assumption, as a reduction of awareness would influence ratings of all domains and not just daily functioning. We presume that this is instead due to a ceiling effect because, in line with the diagnostic criteria, patients with MCI show few limitations in daily functioning (Winblad et al., 2004). Hence, it might be easier to rate the absence of difficulties than to rank them on a 10-point response scale, making discrepancies smaller.

As described above, caregiver burden seems to be more frequently associated with caregiver rating bias than is caregiver depression. We argue that caregiver rating bias can be attributed to the demanding situation to which caregivers are exposed; caring for a person with dementia is associated with physical, emotional, economical, and social costs. According to Zanetti et al. (1999) caregivers' judgments were especially influenced by demands and restrictions on caregivers' time. There are several possible reasons for an association between caregiver rating bias and caregiver burden. One reason could be that caregivers' suffering

fosters a growing intolerance to the patients' symptoms, or that caregivers transfer their own feelings of worry, frustration, fear, etc. into their ratings, inducing an overestimation of the patient's condition (Ready et al., 2004; Sands et al., 2004). Furthermore, observers have been said to give more weight to negative than to positive information, which influences their ratings (Farias et al., 2005). We assume that this effect is more pronounced in burdened caregivers. According to the Attribution Bias Context (ABC) Model (De Los Reyes & Kazdin, 2005) rating discrepancies in childhood psychopathology were caused by disparities among informants' attributions of the causes of the child's behavior. The ABC Model could explain caregiver rating bias in dementia too. Caregiver burden might lead to a differential weighting between environmental and dispositional causes of the patient's behavior. Further longitudinal studies are needed to test the potential explanations.

Several limitations should be taken into consideration. First, caregivers were marginally burdened and depressed. This is not entirely surprising in light of the fact that limited ADL, cognitive impairment, and behavioural problems - variables that are strongly related to caregiver burden and depression - were relatively low in the present sample (Pinquart & Sörensen, 2003; Schoenmakers et al., 2010). Given that only caregivers who feel strongly burdened tend to develop a depression, it is not surprising that MCI- and mild-AD-caregivers are only marginally depressed and do not differ with respect to their depression scores (Clyburn et al., 2000; Ready et al., 2004; Schoenmakers et al., 2010). Consequently, it can be assumed that in samples with a higher degree of severity, results might be more pronounced. Second, it would have been useful to assess the level of patients' awareness to analyze how much variance of the rating discrepancy is explained by the patient's awareness and how much by caregiver burden. In addition, an association between impaired awareness and caregiver burden has been consistently reported in literature too (Clare, Nelis, Martyr, Roberts, et al., 2012). Unfortunately the present study does not explain relationship between

rating discrepancy, caregiver burden and patients' awareness. Third, the patients' neuropsychiatric symptoms were conducted with the NPI (J L Cummings et al., 1994), which is based on informer reports. We realize that integrating caregiver reports as predictors for caregiver rating bias could be confounding. Nevertheless, neuropsychiatric symptoms seem to contribute to rating discrepancy and should therefore be controlled in the regression analysis (Clare, Nelis, Martyr, Roberts, et al., 2012). Finally, a further potential limitation of this study includes the modest sample in relation to the large number of statistical tests carried out. As such, the findings of the present study should be viewed cautiously and replicated in a broader sample.

Despite these limitations, the results of this study have important clinical implications for awareness research and clinical trials, which include caregiver ratings. On the one hand, a dyadic rating discrepancy cannot be directly attributed to reduced patient awareness without controlling for caregiver state. This may explain some of the apparently contradictory findings reported in the awareness literature (Clare, 2004). On the other hand, caregiver reports are a frequently used approach in dementia research (Schulz et al., 2013). The use of caregiver ratings without controlling for caregiver burden can therefore lead to substantial distortions, which might influence diagnosis and therefore type and frequency of treatment. This, in turn, can have negative effects on the patient's health and well-being as well as a considerable impact on healthcare. Due to the strong emphasis of the caregiver rating on implications for patients, it is of major importance to invest resources in caregiver intervention programs.

In summary, this study has provided a comprehensive examination of caregiver rating bias in relation to caregiver burden in MCI and AD. Our findings indicate that dyadic rating discrepancy in depression, apathy, daily functioning, and quality of life seems to be associated with caregiver burden. When caregiver burden is present, data based on caregiver ratings might lead to a substantial caregiver rating bias and thus should be interpreted with caution.

Because caregiver ratings are of high clinical relevance particularly in MCI and AD populations, caregiver burden assessment should be included in clinical practice.

## **5.2 Paper 2: ‘Caregiver perception of apathy in patients with mild cognitive impairment and Alzheimer’s disease: a longitudinal study’**

(Livia Pfeifer, Andrea B. Horn, Andreas Maercker, Simon Forstmeier)

### **5.2.1 Abstract**

**Objective:** Discrepancy between patient and caregiver apathy ratings was examined longitudinally for patients with mild cognitive impairment and Alzheimer’s disease. Particular focus was on the distinction between the positive and negative caregiver bias and its predictive value for a clinical diagnosis of apathy.

**Method:** Apathy rating discrepancy was based on the Apathy Evaluation Scale. Dyads were categorized depending on whether the caregiver reported fewer deficits (positive caregiver bias) or more deficits (negative caregiver bias) than the patient did.

**Results:** Caregiver ratings and rating discrepancy showed a significant increase from baseline to follow-up. By contrast, patient and clinician ratings showed no change across the two time points. Ratings with a negative caregiver bias remained stable, while those with a positive caregiver bias showed a significant increase in the caregiver ratings but also a significant decrease in the patients’ ratings. A negative caregiver bias at baseline was significantly related to greater likelihood of having clinical apathy at follow-up, adjusted for an array of control variables.

**Conclusion:** Positive and negative caregiver bias should be distinguished, as they seem to reflect distinct dyadic processes and are relevant for clinical outcome. Furthermore, negative rating discrepancies can be considered a risk factor for developing apathy.



### 5.2.2 Introduction

Apathy is broadly defined as a lack of motivation and manifests in diminished goal-directed behaviour, goal-directed cognitive activity, and emotions, relative to the patient's previous level of functioning (Robert, Mulin, Malléa, & David, 2010). In mild Alzheimer's disease (AD) and mild cognitive impairment (MCI) it is one of the most common neuropsychiatric symptoms and is considered to be largely independent of depression (Landes et al., 2001; Mortby et al., 2012; Robert et al., 2010). Apathy is related to caregiver burden and fewer positive experiences in caregiving (Brodaty & Burns, 2012; Landes et al., 2001; Onyike et al., 2007). An early occurrence of apathy in MCI or mild AD leads to increased reliance on caregivers to initiate activities that the patient is actually capable of performing alone. Caregivers are lacking an understanding of apathy as an integral part of AD may misinterpret apathetic patients to be withdrawn, insensitive, disinterested, lazy, uncaring, or deliberately oppositional (Colling, 2004). Not surprisingly, these caregivers become frustrated, resentful, and angry, and report significant levels of distress and burden (Colling, 2004; Landes et al., 2001; Politis et al., 2004). Additionally, patients become increasingly withdrawn and passive if caregivers put pressure on the patients and criticize them (Colling, 2004). Apathy measurements are often based on self- and/or caregiver reports to a clinician, who weights the ratings in relation to his or her knowledge (Clarke et al., 2011; Starkstein et al., 2010). Caregivers are a valuable source for diagnosing apathy, given their intimacy with the patient's situation and experiences in everyday life (Dujardin et al., 2008). Consistent with rating discrepancies in other domains, patients' and caregivers' reports of apathy diverge significantly, with a tendency to overestimation on the part of the caregiver, i.e., caregivers generally report more apathy than patients themselves ("overreport"), although they sometimes report less apathy than the patient ("underreport") (Dujardin et al., 2008; Leicht et al., 2010; McKinlay et al., 2008; Pfeifer et al., 2013; Robert et al., 2002). Apathy rating

discrepancies might reflect a combination of patients' downplaying their own suffering and caregivers' overestimating the patient's suffering (Pfeifer et al., 2013). The patients' underestimation may be attributed to anosognosia or cognitive impairment (Horning et al., 2014; Robert et al., 2002; Starkstein et al., 2010). For caregivers, increased burden may lead to endorsing more severe apathy symptoms in cognitively impaired patients; they seem to be less tolerant of patients' suffering than the patients themselves (Dujardin et al., 2008; Pfeifer et al., 2013). This effect has been called *caregiver rating bias* (Pfeifer et al., 2013; Schulz et al., 2013). To our knowledge, no longitudinal study to now has investigated the way in which apathy rating discrepancies in dementia might change over time. Nor has longitudinal development of caregiver ratings in relation to patient ratings been examined; most of the studies on apathy in dementia did not include patient self-reports. Studies on quality of life in dementia, the domain mostly represented in comparing self- and informer ratings, showed that patient ratings do not change substantially until follow-up, whereas caregiver ratings significantly decline (Conde-Sala et al., 2014). Moreover, the same pattern was detected for marital relationship quality in dementia (Clare, Nelis, Whitaker, et al., 2012). The majority of research on the caregiver rating bias either addressed the magnitude of the rating discrepancy or focused on the overreport of a symptom by the caregiver, without considering the reverse, the underreport. Although overreporting a patient's symptom by a caregiver (negative caregiver bias) is more frequent, there is evidence that some caregivers tend to deny the severity of the symptom (positive caregiver bias) (Arguelles et al., 2001; Smeets et al., 2014; Smyth et al., 2002; Tay et al., 2014).

There is some empirical support that the caregiver emotional state and their coping strategies play an important role in the pathogenesis of neuropsychiatric symptoms (García-Alberca et al., 2013). Furthermore, in congestive heart failure patients, for instance, spousal perception of patients' efficacy in coping with the disease predicted patient survival,

independent of patients' self-efficacy judgments (Rohrbaugh et al., 2004). Self-efficacy, the expectations or beliefs about one's own ability to perform actions necessary to produce particular effects, is associated with apathy (Esposito et al., 2014). Esposito et al. (2014) emphasized the importance of giving positive feedback and setting specific performance goals that are attainable in the patient's environment. Hence, caregiver underreports and overreports could be interpreted as efficacy judgments; they may reflect how greatly caregivers support patients' efforts and how greatly they believe in patients' abilities, which could have an impact on the course of patients' apathy. Therefore, we assume that negative caregiver bias could influence the development of apathy.

The present longitudinal study aimed to evaluate caregivers' perception of apathy in contrast to patients' own perception, and the influence of the caregiver bias on the course of apathy. Hence, the study particularly focused on the distinction between the positive and negative caregiver bias and whether the caregiver rating bias predicts clinical apathy at follow-up.

### **5.2.3 Methods**

#### **Sample and Procedure**

The present study was part of the longitudinal study "Motivational Reserve as a Protective Factor in Mild Alzheimer's Dementia and Mild Cognitive Impairment" (MoReA), with participants assessed at entry and reassessed approximately one year, two years, and three years later. The study protocol was approved by the ethics committee of the regional medical authority (No. E-16/2006). A detailed description of the baseline procedures used in the MoReA Study was reported previously (Pfeifer et al., 2013).

For inclusion, participants had to be diagnosed with either MCI or mild AD and had to be age 60 or older. The diagnosis of AD corresponds to the diagnosis of "probable Alzheimer's

disease” according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984). Only mild AD cases with a score of 1 in the Clinical Dementia Rating scale (CDR) (Morris, 1993) and scores between 18 and 26 in the Mini Mental State Examination (MMSE) (Folstein et al., 1975) were included. The MCI diagnosis was based on international consensus criteria (Winblad et al., 2004). Furthermore, each participant needed to be accompanied by a reliable collateral source, usually their spouses (63%). Exclusion criteria were a history of a malignant disease, severe organ failure, metabolic or hematologic disorders, neurosurgery or a neurological condition. Written informed consent was obtained prior to inclusion from all participants and caregivers.

For the present study, data were used from baseline and 12-month follow-up evaluations; the final two follow-ups had not yet taken place at the time of this analysis. 111 dyads were referred to the study and met the eligibility criteria. Of these 111 dyads, 9 refused participation at follow-up, two patients were seriously ill, and three patients were dead. Furthermore, four informers and one patient did not complete the apathy assessment. Complete follow-up data were thus available for 92 dyads (82.9%), 54 patients with MCI and 38 with AD. Mean follow-up period was 13.5 months ( $SD = 2.8$ ). Because the type of diagnosis (MCI / AD) does not seem to affect discrepancy in rating apathy, we did not run analyses separately for both diagnoses. Baseline descriptive and clinical characteristics of the study sample are depicted in Table 7. Mean patient age was 75.1 years; slightly more than half were women. 63.04% participated with their spouses, 23.90% with an adult child, and 13.10% with another relative or friend. A mean MMSE score of 25.49 indicates a low level of cognitive impairment and a mean CSDD score of 3.10 indicates that the patients were on average not depressed. Mean ZBI score was 14.89, indicating that caregivers were on average

only slightly burdened. Mean MMSE score significantly decreased from baseline to follow-up ( $t(91)=2.25$ ,  $p=.027$ ).

### **Measures of apathy**

The Apathy Evaluation Scale (AES) (Marin et al., 1991) was developed for multiple rater sources (self, informant, and clinician) to quantify and characterize apathy in adult patients. The scale comprises 18 items, which are rated on a four-point scale with the following categories: not at all characteristic, slightly characteristic, somewhat characteristic, and very characteristic. Patient (AES-S) and caregiver (AES-I) complete the questionnaire separately. The clinical version (AES-C) is based on a semistructured interview with the patient about a typical day and about hobbies, interests, and plans. Additionally, it entails clinical observations as well as self- and informer reports during the interviews. Cutoff scores for a population with dementia are 36.5, 41.5, and 40.5 for the AES-S, AES-I, and AES-C, respectively (Clarke et al., 2007).

As a second clinician-based measure, the Structured Clinical Interview for Apathy (SCIA) (Starkstein, Ingram, Garau, & Mizrahi, 2005) was used. The interview includes questions assessing the domains of lack of motivation relative to the individual's previous level of functioning (criterion A), lack of effort to perform daily activities (B1), dependency on others to structure activity (B2), lack of interest in learning new things or in new experiences (B3), lack of concern about one's personal problems (B4), and lack of emotional response to positive or negative personal events (B5). Each criterion is assessed with two key questions, followed by additional questions used to rate the severity of symptoms (absent, subclinical, or definitely present). In addition, the extent of social and occupational dysfunction caused by the symptoms of apathy is assessed (criterion C). Criterion D excludes organic causes of behavioral changes other than dementia. Based on the interviews that were conducted separately with the patient and the caregiver, the clinician rated the criteria. Apathy

was diagnosed when the clinician rated a score of 3 (definitely present) on criterion A and on at least three B criteria and a score of 1 (absent) on criteria C and D.

### **Other measures**

The General Self-Efficacy scale (Schwarzer & Jerusalem, 1995) was applied, with parallel forms of the questionnaire given separately to patient and caregiver. This scale refers to patients' global confidence in coping ability across a wide range of demanding or novel situations. It includes 10 items to which participants responded on a four-point scale ranging from 1 (not all true) to 4 (exactly true). Depression was rated by a clinician using the Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos, Abrams, Young, & Shamoian, 1988). The scores of this 19-item scale range from 0 to 38, with higher scores indicating more pronounced depressive symptoms. Caregivers completed the Zarit Burden Interview (ZBI) (Zarit et al., 1980), a 22-item self-report inventory of perceived caregiver strain. Possible scores range from 0 to 88, with higher scores indicating more caregiver burden. To assess depression in caregivers we used the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). The scores of the 15-item scale range from 0 to 45, where higher scores indicate more depressive symptoms.

### **Statistical Analyses**

A discrepancy score for each patient–caregiver dyad was calculated for apathy by subtracting the caregiver-rated AES score from the respective patient-rated score. In keeping with Clare, Nelis, Whitaker, et al. (2012), these raw discrepancy scores were corrected to account for the effect of numerical differences on overall level of scoring by dividing the discrepancy score by the mean of the patient and caregiver score. Finally, dyads were categorized into two groups: “positive caregiver bias” indicates that the caregiver reported fewer deficits than the patient did (positive discrepancy score), and “negative caregiver bias”

that the caregiver reported more deficits than the patient (negative discrepancy score). Excluded from the analyses were dyads with absolute agreement ( $n = 4$ ). We used independent t-tests to compare normally distributed continuous variables with equal variances, Mann-Whitney tests for skewed or inhomogeneous variables, and chi-square tests for categorical variables. Differences between patient-rated and caregiver-rated AES scores were evaluated with an independent t-test. Repeated measures analyses of variance (ANOVA) examined change in patient-rated (AES-S), caregiver-rated (AES-I), and clinician rated (AES-C) apathy, as well as apathy rating discrepancy over the 12-month follow-up, with time as the within-subject factor and the categorical variable positive or negative caregiver bias as the between-subjects factor. In addition, stepwise (likelihood ratio) binary logistic regression analysis was used to identify the impact of the caregiver bias on clinical apathy (SCIA) at follow-up with adjustment for baseline clinical apathy, for patients' age, sex, education, cognitive state, and depression, and for the caregivers' burden and depression. All statistical analyses were performed at an alpha level of 0.05 (two-tailed), using IBM SPSS Statistics 20.0.

#### **5.2.4 Results**

##### **Positive and Negative Caregiver Bias**

Patient and caregiver apathy ratings differed significantly at baseline ( $t(91)=-5.23$ ,  $p < .000$ ) and at follow-up ( $t(91)=-6.66$ ,  $p < .000$ ). At baseline, four dyads (4.35%) showed an absolute rating agreement, 28 (30.43%) a positive rating discrepancy, and 60 (65.22%) a negative rating discrepancy. Excepting the caregiver rating of patient's self-efficacy, there were no significant between-group differences with regard to the positive and negative caregiver bias (Table 7).

Table 7 Patient and caregiver baseline characteristics

| Variable<br><i>n</i>    | Total<br>92  | Agreement<br>4 | Positive bias<br>28 | Negative bias<br>60 | <i>t/Z/χ<sup>2</sup><sup>a</sup></i> | <i>p</i> |
|-------------------------|--------------|----------------|---------------------|---------------------|--------------------------------------|----------|
| Patient                 |              |                |                     |                     |                                      |          |
| Age, y, mean (SD)       | 75.10(8.31)  | 80.00(10.49)   | 72.79(8.05)         | 75.85(8.16)         | -1.65( <i>t</i> )                    | .103     |
| Female, N (%)           | 50(54.35)    | 3(75.00)       | 17(60.71)           | 30(50.00)           | 0.88( $\chi^2$ )                     | .348     |
| Education, y, mean (SD) | 11.96(2.33)  | 12.75(2.36)    | 11.72(2.37)         | 12.01(2.34)         | -0.03( <i>Z</i> )                    | .977     |
| Diagnosis, AD, N (%)    | 38(41.30)    | 2(50.00)       | 10(35.71)           | 26(43.33)           | 0.46( $\chi^2$ )                     | .498     |
| MMSE, mean (SD)         | 25.49(3.25)  | 24.50(4.20)    | 25.75(3.41)         | 25.43(3.15)         | -0.76( <i>Z</i> )                    | .449     |
| Depression, mean (SD)   | 3.10(4.10)   | 0.53(1.06)     | 3.26(3.63)          | 3.20(4.41)          | -0.22( <i>Z</i> )                    | .826     |
| Self-efficacy           |              |                |                     |                     |                                      |          |
| Self, mean (SD)         | 28.17(5.20)  | 29.00(3.56)    | 27.32(6.06)         | 28.51(4.88)         | -.91( <i>t</i> )                     | .367     |
| Caregiver, mean (SD)    | 24.83(6.56)  | 30.28(8.18)    | 27.00(4.32)         | 23.45(6.94)         | 2.49( <i>t</i> )                     | .015     |
| Caregiver               |              |                |                     |                     |                                      |          |
| Age, y, mean (SD)       | 64.65(12.63) | 52.25(20.89)   | 62.79(10.52)        | 66.47(12.48)        | -1.35( <i>t</i> )                    | .180     |
| Female, N (%)           | 67(72.83)    | 4(100.00)      | 19(67.86)           | 44(73.33)           | 0.28( $\chi^2$ )                     | .596     |
| Burden, mean (SD)       | 14.89(12.32) | 8.50(9.98)     | 11.54(8.51)         | 16.93(13.57)        | -1.62( <i>Z</i> )                    | .105     |
| Depression, mean (SD)   | 5.59(6.27)   | 3.00(2.94)     | 4.79(4.14)          | 6.15(7.17)          | -0.44( <i>Z</i> )                    | .658     |
| Relationship            |              |                |                     |                     |                                      |          |
| Spouse N (%)            | 58(63.04)    | 1(25.00)       | 18(64.29)           | 39(65.00)           | 0.00( $\chi^2$ )                     | .948     |
| Child N (%)             | 22(23.90)    | 1(25.00)       | 7(25.00)            | 14(23.33)           | 1.27( $\chi^2$ )                     | .938     |

*Note.* Agreement = apathy discrepancy score equals zero; Positive bias = underreported apathy by the caregiver; Negative bias = overreported apathy by the caregiver; MMSE = Mini-Mental State Examination.

<sup>a</sup>Positive versus negative caregiver bias; *t* = independent t-test, *Z* = Mann-Whitney test,  $\chi^2$  = chi-square test.



## **Longitudinal Analysis**

AES scores (self, informer, discrepancy, and clinician) from the two time points are shown in Table 8. Mean apathy scores at baseline and follow-up were very low (far under the cut-off score) (Clarke et al., 2007). For informer ratings and rating discrepancy, repeated measures ANOVA showed a significant effect of time, with an average increase from baseline to follow-up, and also a significant group effect (i.e., direction of bias). As expected, caregiver ratings of apathy in the group with positive caregiver bias were lower than those in the group with a negative bias; the negative bias reflects an overestimation of symptoms that should be associated with reports of higher scores. By contrast, patient and clinician ratings showed no change across the two time points and no group differences regarding the bias. Significant interaction effects were found in apathy self-ratings and rating discrepancy, and marginally significant effects for informer ratings, which show that changes in rating are especially high for positive caregiver bias. There was no significant difference in the clinician rating of apathy with respect to the two time points and the direction of bias.

Table 8 AES-Scores at baseline and follow-up by direction of baseline apathy discrepancy (positive versus negative caregiver bias)

|                            | Baseline<br><i>M</i> (SD) | Follow-up<br><i>M</i> (SD) | Time <sup>a</sup><br><i>F</i> ( <i>p</i> ) | Group <sup>a</sup><br><i>F</i> ( <i>p</i> ) | Time x<br>Group <sup>a</sup><br><i>F</i> ( <i>p</i> ) |
|----------------------------|---------------------------|----------------------------|--|---|---|
| AES-S                      |                           |                            |  |   |   |
| Total <sup>b</sup>         | 13.65(6.76)               | 13.05(7.08)                | 2.94(.090)                                 | 0.13(.721)                                  | 4.77(.032)  |
| Positive bias <sup>c</sup> | 15.21(6.27)               | 12.17(5.79)                |  |   |   |
| Negative bias <sup>d</sup> | 13.02(6.87)               | 13.38(7.73)                |  |   |   |
| AES-I                      |                           |                            |  |   |   |
| Total <sup>b</sup>         | 18.61(10.89)              | 19.91(11.72)               | 4.15(.045)                                 | 30.02(.000)                                 | 3.76(.056)  |
| Positive bias <sup>c</sup> | 9.82(6.71)                | 13.29(8.13)                |  |   |   |
| Negative bias <sup>d</sup> | 23.14(9.93)               | 23.22(11.98)               |  |   |   |
| AES-(S-I)                  |                           |                            |  |   |   |
| Total <sup>b</sup>         | -0.21(0.66)               | -0.32(0.72)                | 7.04(.010)                                 | 71.88(.000)                                 | 13.27(.000)   |
| Positive bias <sup>c</sup> | 0.56(0.47)                | 0.06(0.81)                 |  |   |   |
| Negative bias <sup>d</sup> | -0.59(0.37)               | -0.51(0.62)                |  |   |   |
| AES-C                      |                           |                            |  |   |   |
| Total <sup>b</sup>         | 17.21(7.74)               | 16.62(8.96)                | 0.97(.329)                                 | 2.65(.107)                                  | 0.28(.597)  |
| Positive bias <sup>c</sup> | 17.96(7.97)               | 17.60(9.54)                |  |   |   |
| Negative bias <sup>d</sup> | 15.64(7.11)               | 14.36(7.54)                |  |   |   |

*Note.* AES = Apathy Evaluation Scale, S = self, I = informer, S-I = rating discrepancy, C = clinician; Positive bias = underreported apathy by the caregiver; Negative bias = overreported apathy by the caregiver.

<sup>a</sup>Analysis of variance for discrepancy group (positive versus negative caregiver rating bias), and time explaining AES scores separately for self, informer, and clinician ratings and for the discrepancy score, ( $df_M/df_R$ )= (1/86). <sup>b</sup> $n = 92$ . <sup>c</sup> $n = 28$ . <sup>d</sup> $n = 60$ .

## Effects of Caregiver Bias on Clinical Apathy

Table 9 displays presence/absence of clinical apathy at baseline and follow-up. Seven patients (7.61%) at baseline and 16 (17.39%) at follow-up met criteria for apathy on the basis of the SCIA. Almost all of these patients belonged to the group with a negative caregiver bias. Over time, there was no significant change for the group with a negative caregiver bias (McNemar:  $p = .115$  and the whole sample (McNemar:  $p = .078$ ).

Table 9 Clinical apathy (SCIA) at baseline and follow-up by direction of apathy discrepancy (positive versus negative caregiver bias)

|                            | Baseline<br>N(%) | Follow-up<br>N(%) |
|----------------------------|------------------|-------------------|
| Total <sup>b</sup>         | 7(7.61)          | 16(17.39)         |
| Positive bias <sup>c</sup> | 0                | 1(1.67)           |
| Negative bias <sup>d</sup> | 7(11.67)         | 15(25.00)         |
| $\chi^2$ (p) <sup>a</sup>  | 3.55(.060)       | 5.89(.015)        |

*Note.* SCIA = Structured Clinical Interview for Apathy; Positive bias = underreported apathy by the caregiver; Negative bias = overreported apathy by the caregiver.

<sup>a</sup> $\chi^2$  (p) = chi-square tests incl. significance values comparing positive vs. negative rating discrepancy. <sup>b</sup> $n = 92$ . <sup>c</sup> $n = 28$ . <sup>d</sup> $n = 60$ .

Results of the binary logistic regression analysis on apathetic versus non-apathetic patients at follow-up are presented in Table 10. A negative caregiver bias was significantly related to greater likelihood of being diagnosed with apathy at follow-up (OR=17.8). Further factors significantly associated with clinical apathy at follow-up were patients' baseline cognitive status (Wald  $\chi^2$ : 8.46,  $df = 1$ ,  $p = .004$ ) and depression (Wald  $\chi^2$ : 6.77,  $df = 1$ ,  $p = .009$ ). Clinical apathy (SCIA) (Wald  $\chi^2$ : 0.093,  $df = 1$ ,  $p = .760$ ) and the remaining control variables showed no such association.

Table 10 Binary logistic regression of negative caregiver bias predicting follow-up clinical apathy (SCIA)

|                      | Wald | Odds Ratio | 95% Confidence Interval | <i>p</i> <sup>a</sup> |
|----------------------|------|------------|-------------------------|-----------------------|
| Model 1 <sup>b</sup> |      |            |                         |                       |
| Negative bias        | 4.29 | 9.00       | 1.13-72.02              | .038                  |
| Model 2 <sup>c</sup> |      |            |                         |                       |
| Negative bias        | 4.45 | 9.69       | 1.20-78.15              | .033                  |
| Model 3 <sup>d</sup> |      |            |                         |                       |
| Negative bias        | 5.35 | 17.80      | 1.55-204.15             | .021                  |

*Note.* *n* = 85. SCIA = Structured Clinical Interview for Apathy; Negative bias = overreported apathy by the caregiver.

<sup>a</sup>Significance values for Wald  $\chi^2$  with *df*=1. <sup>b</sup>Unadjusted. <sup>c</sup>Adjusted for clinical apathy (SCIA) at baseline. <sup>d</sup>Simultaneously adjusted for baseline clinical apathy (SCIA); patients' age, gender (female), education (years), depression (CSDD), MMSE, caregiver burden (ZBI), and caregiver depression (CES-D).

### 5.2.5 Discussion

The aim of the present study was to analyze longitudinally positive and negative caregiver bias and its association with the development of clinical apathy. With respect to changes in apathy rating discrepancy over time, we found that discrepancy increased over the follow-up period, this is in line with previous studies (Conde-Sala et al., 2014; Vasterling, Seltzer, & Watrous, 1997). As reported earlier for discrepancies in rating quality of life and marital relationship in dementia (Clare, Nelis, Whitaker, et al., 2012; Conde-Sala et al., 2014), patients' apathy ratings remained stable while caregiver rated patients' apathy worse at follow-up than at baseline. These findings highlight the necessity to consider the development of self- and informer ratings separately in future longitudinal analyses of rating discrepancy. Clinician rating was situated between the self- and caregiver ratings and remained stable, which is consistent with the literature (Clarke et al., 2007; Colling, 2004). Furthermore, we analyzed changes in apathy ratings according to the direction of caregiver bias at baseline. Our results showed no significant difference between a positive and a negative caregiver

rating bias (i.e., significant group effects) with respect to the clinician rating (AES-C). Thus, taking the clinician rating as a gold standard, it could be assumed that apathy levels were similar in both groups and remained stable over time. Likewise, we did not detect any changes over the follow-up period in the group with a negative caregiver bias. This suggests that the negative caregiver bias is stable over time or that a one-year interval was too short to show any changes. By contrast, the group with a positive caregiver bias showed a significant increase in the caregiver ratings but also a significant decrease in the patients' ratings. Rating discrepancy here approaches zero, which suggests that there may be some adjustment in perception of apathy, possibly resulting from experiences in everyday life or a better understanding of the illness.

Looking at caregiver bias in relation to clinical apathy (SCIA), it becomes apparent that most of the persons diagnosed with apathy belonged to the group with a negative caregiver bias. Our data indicate that caregiver overestimation of the patient's apathy, independent of caregiver burden, seems to be predictive for occurrence of clinical apathy within a year. This might reflect a lack of confidence in the patient and is in line with Rohrbaugh et al. (2004), who showed caregiver confidence as a protective factor in a clinical outcome. On the other hand, the fact that negative caregiver bias predicts clinical apathy at follow-up could reflect the caregivers' diagnostic/prognostic abilities, based on knowledge of the patient's past and present functional abilities. There is considerable evidence that caregivers are a valuable source in apathy diagnosis and have a good predictive validity (Clarke et al., 2007; Dujardin et al., 2008; Marin et al., 1991). Our findings indicate an effect of the caregiver's judgments on the course of the patient's apathy above and beyond known relevant variables. Caregivers who are confident and tend to minimize difficulties on the part of the patient could have a positive impact on the occurrence of apathy. This assumption is supported by the finding that informer-rated self-efficacy was higher in the group with positive than with negative

caregiver bias; notably, self-ratings by the patients did not differ between the groups (see Table 7). A previous study on motivational processes in depression found self-efficacy to be a mediator between social support and depression in cognitively impaired individuals (Fankhauser et al., 2014). Its authors discussed social support in the form of coping assistance, i.e., providers of social support help the receiver cope successfully with stressful situations. Finally, other interpersonal processes in which both patient and caregiver interact could also directly or indirectly contribute to apathy. Future studies are needed to clarify the relationship between caregivers' perception of illness and patients' motivational abilities and to better understand dyadic coping mechanisms in apathy.

The strengths of this study are its prospective longitudinal design, its precise diagnosis of apathy according to published criteria, and the relatively low drop-out rate. Longitudinal studies are particularly important for progressive illnesses such as dementia. Furthermore, the distinction between positive and negative caregiver bias and first evidence of an association with clinical outcome are a novel contribution to the field. However, several limitations of the present study should be mentioned. First, the mean rate of apathy in the current sample was far under the cut-off level of a clinically significant syndrome. However, prevalence of clinical apathy (SCIA) at baseline complied with the scores of a sample including people with MCI and mild dementia (Onyike et al., 2007). Further research is required with a sample of people having higher apathy scores and an assessment at multiple time points and with a longer time interval to replicate the current findings. Second, analogous to Tay et al. (2014), we categorized a rating discrepancy of zero as agreement, but presume that discrepancies close to zero could also be considered agreement. Further methodological studies are necessary to evaluate the intersection between agreement and bias. Third, it would have been useful to assess the level of patients' awareness of apathy to analyze to what extent this is a risk factor for apathy. Starkstein et al. (2010) found that apathy in AD (based on caregiver

ratings) is significantly predicted by anosognosia. However, their anosognosia measurement was based on the discrepancy between the self- and informer rating of daily activities, mood, and behavior. It is thus uncertain whether anosognosia plays a role in our results.

Despite these limitations, the results of this study have important clinical implications. Regardless of whether caregivers are accurate or biased in their perceptions, negative rating discrepancies can be a warning sign or risk factor for developing apathy. Clinicians should be especially cautious if a negative caregiver bias is present. However, the present study underscores the importance of understanding the way the patient and caregiver converge in their perception of apathy and has implications for how to plan interventions. Intervention programs should provide specific counselling for caregivers to reinforce positive perceptions of the relationship with the apathetic patients, and they should include strategies to motivate patients to become more active to prevent the development of apathy (de Vugt et al., 2003).

In conclusion, our findings support the need for distinguishing between positive and negative caregiver bias, as the biases seem to reflect distinct underlying dyadic processes. Furthermore, our findings highlight the importance of the caregiver's perception of apathy for the course of the patient's illness as it might facilitate earlier identification of individuals at risk for clinical apathy.

### **5.3 Paper 3: ‘Impaired awareness of apathy in mild Alzheimer’s disease: process and effect of a multicomponent cognitive-behavioural treatment’**

(Livia Pfeifer, Andrea B. Horn, Tanja Roth, Egemen Savaskan, Andreas Maercker, Simon Forstmeier)

#### **5.3.1 Abstract**

**Background:** Earlier research has shown that impaired awareness of deficits may limit therapeutic outcome, but it remains unclear how awareness predicts the therapeutic process and if awareness is changeable through a psychosocial intervention for dementia. In this study we evaluated the process and the effect of a multicomponent cognitive-behavioural treatment (CBT) in relation to impaired awareness of apathy in a randomised controlled trial in patients with mild Alzheimer’s disease.

**Methods:** Participants of the CBT group (n=17) received a treatment comprising different modules (diagnosis and goal setting; psychoeducation; engagement in pleasant activities; cognitive restructuring; live review; couples counselling) that targeted reduction of neuropsychiatric symptoms and involved approximately 18 sessions. The comparison group (n=12) received treatment as usual. Awareness of apathy was assessed by a discrepancy score; the parallel caregiver score has been subtracted from the total patient score of the Apathy Evaluation Scale.

**Results:** The CBT group showed a significant negative correlation between global alliance and impaired awareness of apathy, indicating that the more awareness was impaired the more negative the patient rated the therapeutic alliance. Awareness of apathy, as measured by discrepancy of ratings between patient and caregiver, remained stable in the CBT condition and decreased significantly in the control condition. This change can be attributed



to an increase in the patients' apathy ratings, whereas the caregiver ratings remained stable over time.

Conclusion: Impaired awareness of apathy in patients with Alzheimer's disease seems to play a decisive role for important factors in psychological treatment like therapeutic alliance.

### **5.3.2 Introduction**

Awareness of deficits, defined as the capacity to discern the true nature of the situation, or the recognition of the fact, degree, and implications of one's own illness (Zanetti, Vallotti, et al., 1999), is often impaired in Alzheimer's disease (AD) and can affect different domains, e.g. cognitive, emotional, and social functioning (Ecklund-Johnson & Torres, 2005; Nelis et al., 2011; Vogel et al., 2010). Research has shown that awareness of dementia related symptoms varies across domains (Ecklund-Johnson & Torres, 2005; Leicht et al., 2010; Pfeifer et al., 2013).

Most of the studies focus on the domains of memory, executive dysfunctions, and ADL (Ecklund-Johnson & Torres, 2005), but studies with a focus on apathy are relatively underrepresented. Leicht et al. (2010) reported impaired awareness of apathy in AD as measured by questionnaire discrepancies between carers' informer ratings and patients' self-ratings; the discrepancies seem to be similar to those reported regarding ADL and recent memory. The calculation of discrepancy scores is a main approach for assessing awareness of deficits in dementia. Accordingly, the degree of impaired awareness has been operationally defined as the discrepancy between the patient's self-rating of functioning on a given measure and the carer's rating of the patient's functioning on a parallel measure (Clare, 2004). This approach relies on the expectation that relatives are reliable informants. This has been questioned in previous studies, since e.g. caregiver burden is a significant predictor of rating discrepancy with regards to apathy which could be interpreted as reflecting biases from the

caregiver's perspective (Nelis et al., 2011; Pfeifer et al., 2013; Stella et al., 2015). Accordingly, it has been suggested that these caregiver biases might be reflected in over- or underestimating symptoms as compared to the patient's perspective which are associated with significant differences in outcome (Pfeifer, Horn, Maercker, & Forstmeier, n.d.).

To our knowledge, there have been just a few attempts to examine the relationship between awareness in dementia and any kind of intervention. Some studies analysed reduced awareness of deficits as a predictor of the outcome of a cognitive intervention in AD and suggest that impaired awareness may limit therapeutic outcome (Clare et al., 2004; Fernández-Calvo et al., 2015; Koltai et al., 2001). In contrast to these findings, another study showed that the more frequently patients with mild cognitive impairment perceived memory failures, the less motivated they were to participate in a cognitive training (Werheid, Ziegler, Klapper, & Köhl, 2010). Likewise, in individuals with neuropsychiatric symptoms after acquired brain injury an association between awareness and treatment motivation was not confirmed (Smeets et al., 2014). The biopsychosocial approach by Ownsworth et al. (2006) proposes a relative and interactive influence of neuro-cognitive, psychological, and socio-environmental factors for explaining awareness of AD related symptoms. Factors of the psychological (e.g. denial and coping style) and social level (e.g. stigma, exclusion, and social desirability) could complicate the therapeutic work and consequently impair the therapeutic outcome (Ownsworth et al., 2006). Otherwise a trusting therapeutic relationship could provide a secure environment for the patient that may enable overcoming these defence mechanisms and may enhance patients' compliance in therapy, which is prerequisite for therapy success (Schönberger et al., 2006).

Studies on change of awareness by a treatment in other diseases reported mixed results (Connolly Gibbons, Crits-Christoph, Barber, & Schamberger, 2007). Schrijnemaekers, Smeets, Ponds, van Heugten, & Rasquin (2014) provided an overview about treating

unawareness in patients with acquired brain injury. They concluded that impaired awareness of symptoms could be improved through a combination of education and multimodal feedback related to performance. Moreover, treatments targeting awareness of dementia related symptoms might be recommended for several reasons. Various researchers have demonstrated a positive correlation between impaired awareness of deficits and neuropsychiatric symptoms as well as caregiver burden (Horning et al., 2014; Turró-Garriga et al., 2013; Vogel et al., 2010). Thus, it could be possible that an increase of awareness has a positive effect on relevant variables like neuropsychiatric symptoms or caregiver burden. In addition, individuals with impaired awareness showed less therapy motivation, resisted support or treatment recommendation, set unrealistic goals, developed fewer compensatory strategies, and benefited in general less from a treatment (Ownsworth & Clare, 2006). Therefore, there are reasons to believe that important general features of the therapeutic process like therapeutic alliance, self-esteem, mastery, clarification, session-outcome, bond, control, and problem actuation should be altered if there is a lack of awareness of the problem. Therefore, raising awareness of deficits may enhance patients' compliance and self-efficacy, and enlarge the repertoire of behaviours toward self and others, which in turn can have an influence on the success of a treatment (Grosse Holtforth et al., 2007; Schönberger et al., 2006). On the other side, if the lack of awareness was reflecting a defensive coping strategy, an increase in awareness could possibly also have an adverse effect on the patients' mood and functioning. Findings, however, have indicated that the process of developing awareness of deficits during rehabilitation was not associated with heightened emotional distress (Ownsworth & Clare, 2006).

In the present study we aimed to elucidate some answers about the process and effect of a psychosocial multicomponent treatment in early-stage AD in relation to awareness of apathy, assessed by a patient-caregiver discrepancy score. The cognitive behavioural treatment (CBT)

consisted of eight modules (i.e., diagnosis and goal setting; psychoeducation; engagement in pleasant activities; cognitive restructuring; live review; behaviour management; interventions for the caregiver; couples counselling). First, we expect that patients with more impaired awareness would rate the quality of the therapy sessions lower than patients with intact awareness. Furthermore these ratings of the therapy sessions could differ regarding different facets of the therapeutic process (i.e., therapeutic alliance, self-esteem, mastery, clarification, session-outcome, bond, control, and problem actuation) and the modules. Some modules might be more aversive because awareness is confronted, some might be more helpful because the patients feel understood and notice progress, and some might be irrelevant for the therapeutic process. Second, we assume that the present CBT-based treatment could raise awareness in apathy, even though the treatment was not originally designed to affect awareness, but neuropsychiatric symptoms in general. Furthermore the treatment includes multimodal feedback of symptoms. Therefore and also because the intensive reflection and confrontation with one's situation could change perception concerning the abilities and symptoms, we hypothesise that awareness of apathy rises.

### **5.3.3 Methods**

#### **Design and Procedures**

For the present study we used baseline and post-intervention data from an ongoing longitudinal randomised controlled trial, the 'Cognitive-behavioural treatment for patients with mild AD and their caregivers' (CBTAC), which is described in more detail elsewhere (Forstmeier et al., n.d.). The study protocol was approved by the cantonal ethic commission of Zurich, Switzerland (No. 2009-0078/3).

We rest our sample size calculation on the conservative assumption of a small-to-medium effect size for depression ( $d = 0.5$ ,  $f = 0.25$ ). Given an  $\alpha = 0.05$  and a test power  $1 - \beta = 0.80$ , a

total sample size of  $n = 46$  is required to test the condition x time interactions in an ANOVA with repeated measurements ( $r = 0.3$ ). Enrolment into the study started in January 2011 and data collection will be completed in autumn 2016.

Before entering the study, an interdisciplinary team assigned the diagnosis after thorough neurological, psychiatric, clinical (including neuroimaging) and neuropsychological assessments. Participants who met study criteria and gave informed consent were assigned at random to either CBT or treatment as usual (TAU). Randomisation was performed by computer algorithm, independently operated by the Clinical Trials Center (CTC) of the University Hospital Zurich. Emotional and behavioural problems of the patient and the caregiver were assessed separately by blinded psychologists and the cognitive state of the patient by a neuropsychologist at baseline and in the CBT group at post-intervention and in the TAU group approximately one year after baseline.

## **Participants**

Participants were recruited by the Gerontopsychiatric Clinic of the Psychiatric University Hospital Zurich and via advertisements and articles in the local media. Participants had to meet NINCDS-ADRDA criteria for probable or possible AD (McKhann et al., 1984), including persons with mixed AD and vascular dementia. Only mild cases with a score of 0.5 or 1 on the Clinical Dementia Rating scale (CDR) (Morris, 1993) and a score of at least 20 on the Mini-Mental State Examination (MSME) (Folstein et al., 1975) were included. Furthermore the participants had to suffer from any neuropsychiatric symptoms, in particular depression, apathy, anxiety, and other symptoms. Additionally, each participant needed to be accompanied by a caregiver, for instance a family member or a close friend, who had to be available to take part in most of the sessions and was responsible for reminding the patient of therapy tasks. Exclusion criteria were a concomitant alcohol or drug addiction and a history of

a malignant disease, severe organ failure, metabolic or hematologic disorders, neurosurgery or neurological conditions.

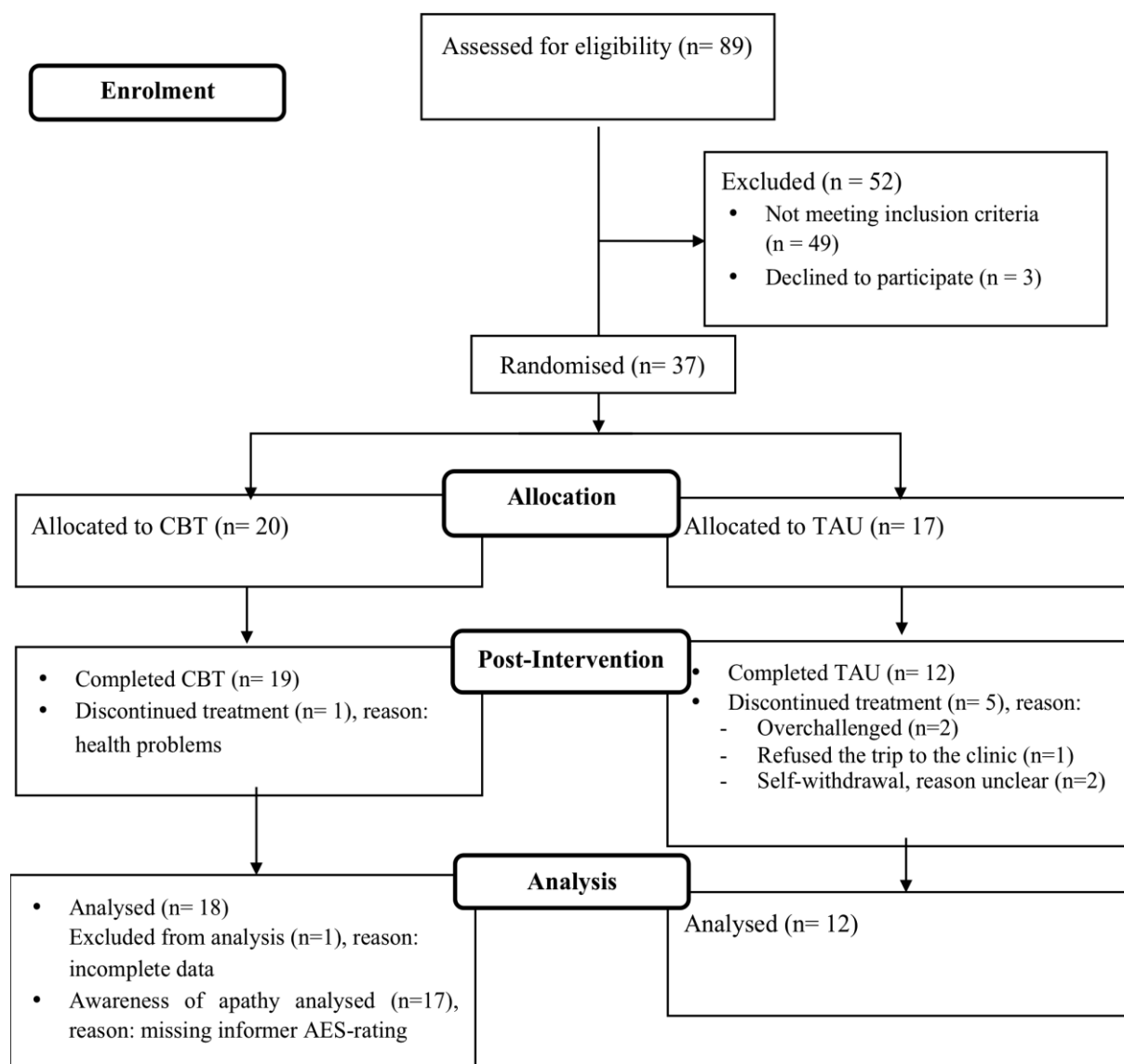


Figure 3. Participant flow diagram. Recruitment was undertaken from 2010 to 2014, interventions were conducted since 2011 and are still on going.

## **Treatment**

The CBT consisted of eight modules and target reduction of neuropsychiatric symptoms of the patients as well as burden and depressive symptoms of the caregivers. Table 11 presents a summary of the eight modules: (1) diagnosis and goal setting, (2) psychoeducation, (3) engagement in pleasant activities, (4) cognitive restructuring, (5) live review, (6) behaviour management, (7) interventions for the caregiver, and (8) couples counselling. For more details on the interventions see Forstmeier et al. (2015). The 50-minute CBT sessions were carried out on average every second week by experienced psychotherapists. The numbers of sessions per module and the presence of the caregiver were adjusted based on the individual needs of the patient by the therapist. A short form of the Bern Post Session Report–Patient Form (BPSR-P) (Flückiger, Regli, Zwahlen, Hostettler, & Caspar, 2010) was completed after every session, on condition that the patient was capable and willing. TAU is defined as receiving at least three out of the six following interventions: psychoeducation, appropriate medical treatment, social counselling, memory training, patients’ self-help group, caregivers’ self-help group.

Table 11 Description of the modules of the CBT

| Nr. | Module                              | Activities   |
|-----|-------------------------------------|--|
| 1   | Diagnosis and goal setting          | Diagnosis of emotional and behavioural problems of patient and caregiver, and behaviour analysis (situation, behaviour, emotion, cognition, and consequences) were carried out. Furthermore the individual goal setting and the scheduling of the sessions were included. The therapeutic alliance was developed during this phase and motivation for change was encouraged.                             |
| 2   | Psychoeducation                     | The therapist provided information about the diagnosis of AD, its causes, course, pharmacological and psychosocial treatment options, information on adopting external memory aids, and support to the patient and the caregiver.  |
| 3   | Engagement in pleasant activities   | The patient was helped to increase number and frequency of pleasant activities and adopt a structured weekly schedule. Social, physical, and other leisure activities were included.   |
| 4   | Cognitive restructuring             | Dysfunctional thoughts (depression, anxiety, or anger related) were recorded, discussed, and alternative, helpful thoughts were practiced.   |
| 5   | Life review                         | In each life review session, one or two of Erikson's stages (Erikson, 1950) were applied to the life of the patient. The patient was guided chronologically through life experiences and was encouraged to evaluate them. Photographs, music, and other objects were used to support reminiscence.   |
| 6   | Behaviour management for caregivers | Strategies to change precursors and consequences were planned and trained with the caregiver.  |
| 7   | Interventions for caregiver         | Interventions with the aim to improve caregiver's wellbeing, stress management and emotion regulation (e.g., anger management), and social support were delivered to the caregiver in sessions mainly without the patient and parallel to the sessions with the patient. Interventions from modules 3 and 4 were used. The focus of this module was on the caregiver and not on the patient or the dyad. |
| 8   | Couple Counselling                  | Sessions focused on expressing fears, adapting to new roles, improving communication and joint coping, establishing joint activities, and planning for the future were included. To help the couple talk about the relationship and develop a positive attitude towards couples counselling, the oral history interview was used.  |

## Measures

Awareness of apathy was assessed by the subtraction of the total patient score of the Apathy Evaluation Scale (AES) (Clarke et al., 2007) from the total caregiver score; this means, the higher the resulting apathy discrepancy score the less awareness. The AES was



developed for multiple rater sources (self, informant, and clinician) to quantify and characterise apathy in adult patients. The scale comprises 18 items, which are rated on a four-point scale with the following categories: not at all characteristic, slightly characteristic, somewhat characteristic, and very characteristic. Patient and caregiver completed the questionnaire separately.

For a clinical rating of lack of awareness, we used the Clinical Insight Rating (CIR) (Leicht et al., 2010; Ott & Fogel, 1992). It consists of four items that cover the patient's insight of (1) the reason for the visit to the clinic, (2) cognitive deficits, (3) functional deficits, and (4) progression of AD symptoms. Based on separate semi-structured interviews with the patient and caregiver, the clinician rates the level of insight (full, partial, and no insight) and builds a total sum-score between 0 and 8.

The Bern Post Session Report–Patient Form (BPSR-P) (Flückiger et al., 2010) assesses central aspects of the therapeutic process from the patient's perspective. The scale comprises 22 items, which are rated on a 7-point Likert scale ranging from -3 (not at all) to 3 (yes, exactly). We adapted the questionnaire to a sample of cognitively impaired elderly persons, just using the item per subscale with the highest factor loading (8 items). BPSR-P subscales and their respective item are: global alliance ('The therapist and I understand each other'), self-esteem experiences ('The therapist lets me feel my strengths'), mastery ('Now I feel better prepared for situations that I could not handle before'), clarification ('I feel that I have a better understanding of myself and my problems'), session outcome ('Today, we made substantial progress in the therapy session'), contentment of the bond ('I think the therapist's view of my problems is too simple'), control ('I can decide what we discuss in the session'), and problem actuation ('I was very emotionally involved in today's session').

Depression was rated by a clinician using the Cornell Scale for Depression in Dementia (CSDD) (Alexopoulos et al., 1988). The scores of this 19-item scale range from 0 to 38, with

higher scores indicating more pronounced depressive symptoms. Caregivers completed the Zarit Burden Interview (ZBI) (Zarit et al., 1980), a 22-item self-report inventory of perceived caregiver strain. Possible scores range from 0 to 88, with higher scores indicating more caregiver burden. The Mini Mental State Examination (MMSE) (Folstein et al., 1975) was used as a measure for the global level of cognitive functioning.

## **Data Analyses**

Baseline differences between the intervention and the control group were analysed by independent *t*-tests for continuous variables and chi-square tests for categorical variables. To examine the therapeutic process from the patient's perspective we computed mean levels across sessions per module of the corresponding subscales of the BPSR-P. Since in small samples *p*-values are not convincing to dichotomise significant or non-significant results and do not allow for the comparison of effect sizes, we used Fisher's *z*-transformation for comparing the size of correlations between awareness of apathy and the therapeutic process from the patients' perspective per module (Meng, Rosenthal, & Rubin, 1992). Furthermore, the overlap of 95% confidence intervals of the Fisher *z*-values enables conclusions about statistical significant differences between different associations. The effect of the treatment was analysed using repeated-measures analyses of variance (ANOVAs) with groups (CBT, TAU) as the between-subjects factor and time (baseline, post-intervention) as the within-subjects factor. In small samples it is preferred only to control ANOVA for the differences between groups that are not equated through randomisation (Hilgeman et al., 2014). After verifying successful randomisation we did not use any control variables for the ANOVAs. To explore the change in rating discrepancy, we also analysed intervention effects of apathy both self and caregiver ratings, and the clinical insight rating. Effect sizes (Cohen's *d*) were used as the primary indicator of likely treatment effects in this small sample: *d* = 0.2 was taken to indicate a small, *d* = 0.5 a moderate, and *d* = 0.8 a large effect. Effect sizes greater or equal to

0.5 (a medium effect) will be interpreted as potentially meaningful. Differences reflected in group x time interactions were explored with post-hoc within-group *t*-tests.

Recent literature has suggested that positive and negative rating discrepancies should be distinguished as they seem to reflect distinct dyadic processes (Pfeifer et al., n.d.; Smeets et al., 2014). Therefore we compared patients with a positive rating discrepancy to those with a negative one regarding the change in apathy rating discrepancy. The CBT group consisted of 1 patient with a negative rating discrepancy and 16 patients with a positive rating discrepancy ( $Z = -0.615$ ,  $p = 0.538$ ) and the TAU group of 2 patients with a negative rating discrepancy and 10 patients with a positive rating discrepancy ( $Z = -1.194$ ,  $p = 0.232$ ). Because the direction of the rating discrepancy did not seem to affect the therapy effect, we waived considering the distinction for further analyses. All statistical analyses were performed with an  $\alpha$  level of 0.05 (two-tailed), using IBM SPSS Statistics 20.0.

#### **5.3.4 Results**

The flow of participants is described in Figure 3. As shown in Table 12, there were no significant differences at baseline between CBT ( $n = 18$ ) and TAU ( $n = 12$ ) regarding the demographic, neuropsychiatric, and outcome variables.

Bivariate correlations among rating discrepancy in apathy and the other study variables are also given in Table 12. We found a marginally significant correlation between awareness of apathy and the clinical insight rating ( $r = .34$ ,  $p = .070$ ). Significant correlations were observed between awareness of apathy and apathy caregiver rating ( $r = .83$ ,  $p < .001$ ), also between apathy caregiver rating and apathy self-rating ( $r = .44$ ,  $p = .018$ ), MMSE ( $r = -.41$ ,  $p = .049$ ), as well as caregiver burden ( $r = .41$ ,  $p = .028$ ). Furthermore there was a significant correlation between patients' depression and gender ( $r = -.48$ ,  $p = .009$ ), with higher depression in men.

Table 12 Participants' baseline characteristics and bivariate correlations among them

|                            | 1     | 2    | 3     | 4      | 5    | 6    | 7    | 8   | 9 | CBT ( <i>n</i> = 17)<br><i>M</i> ( <i>SD</i> ) or <i>N</i> (%) | TAU ( <i>n</i> = 12)<br><i>M</i> ( <i>SD</i> ) or <i>N</i> (%) | <i>t</i> / $\chi^2$ <sup>a</sup> |
|----------------------------|-------|------|-------|--------|------|------|------|-----|---|--|--|----------------------------------|
| 1. Awareness of apathy     | 1     |      |       |        |      |      |      |     |   | 8.14(10.13)  | 7.20(10.67)  | .811                             |
| 2. Apathy, self            | -.14  | 1    |       |        |      |      |      |     |   | 13.42(6.75)  | 14.72(5.72)  | .591                             |
| 3. Apathy, caregiver       | .83** | .44* | 1     |        |      |      |      |     |   | 21.56(11.89)   | 21.92(10.66)   | .934                             |
| 4. Depression              | -.01  | -.14 | -.09  | 1      |      |      |      |     |   | 6.94(4.04)   | 4.85(3.45)   | .157                             |
| 5. Age, y                  | .26   | -.15 | .15   | -.22   | 1    |      |      |     |   | 74.33(8.20)  | 74.25(9.53)  | .980                             |
| 6. Gender (female)         | -.08  | -.10 | -.13  | -.48** | .26  | 1    |      |     |   | 12(66.7%)  | 9(75%)   | .626                             |
| 7. MMSE                    | -.29  | -.30 | -.41* | .18    | -.12 | -.27 | 1    |     |   | 25.29(2.95)  | 24.36(2.16)  | .394                             |
| 8. Clinical insight rating | .34   | .01  | .31   | -.23   | .28  | .16  | -.21 | 1   |   | 2.83(2.64)   | 3.08(2.58)   | .799                             |
| 9. Caregiver burden        | .27   | .29  | .41*  | -.01   | .24  | .23  | -.08 | .09 | 1 | 24.25(8.56)  | 30.39(13.30)   | .134                             |

*Notes:* Pearson correlations (between two continuous variables), point-biserial correlations (between a continuous and a dichotomous variable). *t*,  $\chi^2$ : values of statistics from the paired t-tests (with standard deviation) and chi-square tests; *SD*: standard derivation; CBT: Cognitive behavioural treatment; TAU: Treatment as usual. MMSE: Mini-Mental State Examination; Awareness of apathy: Discrepancy between apathy caregiver rating (apathy, caregiver) and apathy patient rating (apathy, self). \**p*<.05, \*\**p*<.01.

Table 13 Total scores of the Bern Post Session Report–Patient Form and bivariate correlations between them and awareness of apathy. Z-scores transformed bivariate correlations between impaired awareness of apathy and the subscales of the Bern Post Session Report–Patient Form and 95% confidence intervals.

|                      | Total<br>n=13 | <i>M</i> (SD)<br>n=13 | M1: Goals<br>Z, 95%CI<br>(n=12) | M2: Psycho-<br>education<br>Z, 95%CI<br>(n=11) | M3:<br>Activities<br>Z, 95%CI<br>(n=10) | M4: CR<br>Z, 95%CI<br>(n=7) | M5: Life<br>review<br>Z, 95%CI<br>(n=12) | M8: Couples<br>Z, 95%CI<br>(n=7) |
|----------------------|---------------|-----------------------|---------------------------------|--|---|-----------------------------|--|----------------------------------|
| Global alliance      | -.747**       | 2.13(0.57)            | -0.94<br>[-1.60, -0.29]         | -0.71<br>[-1.40, -0.02]                        | -1.13<br>[-1.87, -0.39]                 | -0.16<br>[-1.14, 0.82]      | -0.54<br>[-1.20, 0.11]                   | -0.84<br>[-1.82, 0.14]           |
| Self-esteem          | -.365         | 1.45(0.60)            | -0.71<br>[-1.36, -0.05]         | -1.20<br>[-1.89, -0.51]                        | -0.14<br>[-0.88, 0.60]                  | 0.37<br>[-0.61, 1.35]       | -0.44<br>[-1.09, 0.21]                   | -0.39<br>[-1.37, 0.59]           |
| Mastery              | .076          | 0.56(0.48)            | 0.06<br>[-0.60, 0.71]           | 0.18<br>[-0.51 / 0.87]                         | 0.06<br>[-0.68, 0.80]                   | 0.28<br>[-0.70, 1.26]       | -0.12<br>[-0.77, 0.53]                   | -0.44<br>[-1.42/0.54]            |
| Clarification        | -.244         | 1.12(0.57)            | -0.51<br>[-1.17, 0.14]          | -0.21<br>[-0.91, 0.48]                         | 0.69<br>[-0.05, 1.43]                   | 0.07<br>[-0.91, 1.05]       | 0.01<br>[-0.64, 0.66]                    | -0.44<br>[-1.42, 0.54]           |
| Outcome              | -.328         | 1.23(0.45)            | -0.13<br>[-0.78, 0.52]          | -0.49<br>[-1.18, 0.20]                         | -1.08<br>[-1.82, -0.34]                 | 0.30<br>[-0.68, 1.28]       | -0.12<br>[-0.77, 0.53]                   | -0.31<br>[-1.29, 0.67]           |
| Bond <sup>a</sup>    | -.087         | 0.00(1.45)            | 0.34<br>[-0.31, 0.99]           | 0.30<br>[-0.39, 0.99]                          | 0.05<br>[-0.70, 0.79]                   | 0.78<br>[-0.2, 1.76]        | 0.18<br>[-0.48, 0.83]                    | -1.67<br>[-2.65, -0.69]          |
| Control              | -.399         | 0.94(0.92)            | -0.29<br>[-0.94, 0.37]          | -0.72<br>[-1.42, -0.03]                        | -0.10<br>[-0.84, 0.64]                  | 0.24<br>[-0.74, 1.22]       | -0.28<br>[-0.93, 0.38]                   | 0.13<br>[-0.85, 1.11]            |
| Problem<br>actuation | .045          | 0.81(0.69)            | 0.05<br>[-0.61, 0.70]           | 0.10<br>[-0.59, 0.80]                          | -0.06<br>[-0.80, 0.68]                  | 0.48<br>[-0.50, 1.46]       | 0.15<br>[-0.51, 0.80]                    | 0.27<br>[-0.71, 1.25]            |

*Notes:* Including mean scores per module and per patient of the CBT-group. The higher the rating discrepancy in apathy between patient and caregiver, the more awareness was impaired. CR: Cognitive restructuring. \*p<.05, \*\*p<.01.

<sup>a</sup>Reversing the polarity of the subscale ‘Bond’ made the values more comparable to those of the other subscales.

## **Therapeutic Process**

Patients in the CBT group completed an average of 17.86 (4.42) sessions. Correlations between the subscales of the BPSR-P and awareness of apathy are shown in Table 13. We observed a significant negative correlation between mean levels across all sessions of the subscale global alliance and impaired awareness of apathy ( $r = -.747, p = .007$ ). All Fisher  $z$ -transformed correlations and 95% confidence intervals per subscale and per module are displayed in Table 13.

For differences regarding the association of awareness-self-esteem we detected a confidence interval overlap of only 0.1 for the module psychoeducation ( $z = -1.2$ , 95% CI [-1.89, -0.51]) and cognitive restructuring ( $z = 0.37$ , 95% CI [-0.61, 1.35]). This suggests a marginally significant difference between the two correlations, pointing at differential effects of the modules. The higher the measure of impaired awareness the lower the self-esteem after the psychoeducation sessions; in contrast after the sessions targeting cognitive restructuring self-esteem was positively associated with unawareness. Furthermore the subscale ‘bond’ in couples counselling differed significantly from the remaining modules ( $z = -1.67$ , 95% CI [-2.65, -0.69]); there was an outstanding negative correlation between impaired awareness in apathy and the appraisal that the therapists underestimated the complexity of patients’ problems as measured in the subscale ‘contentment with bond’.

## **Effect on awareness**

As shown in Table 14, there was a significant intervention effect on awareness of apathy (time x group:  $F(1,28) = 5.437, p = .027, d = 0.899$ ). Within-group  $t$ -test showed that awareness of apathy remained constant in the CBT ( $t(29) = -0.989, p = .337$ ) and decreased in the TAU condition ( $t(29) = 2.426, p = .034$ ). Apathy self-ratings showed a moderate treatment effect ( $F(1,28) = 2.552, p = .122, d = 0.614$ ) and post-hoc tests showed a marginally

significant increase in apathy self-ratings in the TAU condition ( $t(29) = -2.173, p = .052$ ) but not in the CBT condition ( $t(29) = 0.218, p = .830$ ). The caregiver apathy rating ( $F(1,28) = 0.497, p = .487, d = 0.271$ ) and the clinical insight rating ( $F(1,28) = 0.039, p = .845, d = 0.063$ ) did not show time x group interactions.

Table 14 Relevant study variables (means and standard deviations) for the CBT and TAU conditions at baseline and at post-intervention as well as treatment effects

|                                |                        |                                  | Time x Group |                                    |          |                    |
|--------------------------------|------------------------|----------------------------------|--------------|------------------------------------|----------|--------------------|
|                                | CBT<br>( <i>n</i> =17) | TAU Condition<br>( <i>n</i> =12) | <i>F</i>     | df <sub>M</sub> /df <sub>R</sub> : | <i>p</i> | Cohens<br><i>d</i> |
| <i>Awareness of apathy</i>     |                        |                                  | 5.437        | 1/27                               | .027     | 0.899              |
| Baseline                       | 8.14(10.13)            | 7.20(10.67)                      |              |                                    |          |                    |
| Post-intervention              | 9.22(8.85)             | 4.58(9.26)                       |              |                                    |          |                    |
| <i>Apathy, self</i>            |                        |                                  | 2.552        | 1/27                               | .122     | 0.614              |
| Baseline                       | 13.42(6.75)            | 14.72(5.72)                      |              |                                    |          |                    |
| Post-intervention              | 13.68(6.49)            | 17.78(7.29)                      |              |                                    |          |                    |
| <i>Apathy, caregiver</i>       |                        |                                  | 0.497        | 1/27                               | .487     | 0.271              |
| Baseline                       | 21.56(11.89)           | 21.92(10.66)                     |              |                                    |          |                    |
| Post-intervention              | 22.90(10.91)           | 22.36(9.47)                      |              |                                    |          |                    |
| <i>Clinical insight rating</i> |                        |                                  | 0.039        | 1/28                               | .845     | 0.063              |
| Baseline                       | 2.83(2.64)             | 3.08(2.58)                       |              |                                    |          |                    |
| Post-intervention              | 3.17(2.46)             | 3.25(2.49)                       |              |                                    |          |                    |

Notes: CBT: Cognitive behavioural treatment; TAU: Treatment as usual.

### **5.3.5 Discussion**

#### **Therapeutic Process**

First, we explored the relationship between impaired awareness of apathy and various components of the therapeutic process from the patients' view. Results showed a significant negative correlation between global alliance and impaired awareness of apathy across all sessions, indicating that the more awareness was impaired the more negatively the patient assessed the therapeutic alliance. The therapeutic alliance is considered to be an important aspect of successful treatment and has been found to be a consistent predictor of therapy outcomes in a variety of mental disorders (Castonguay et al., 2006). Therefore, impaired awareness could possibly lead to a worse intervention outcome via lower therapeutic alliance.

The comparison of the modules indicated differences in effects on self-esteem between the modules psychoeducation and cognitive restructuring. Higher levels of impaired awareness were associated with lower levels of self-esteem as measured during the therapy in psychoeducation sessions while in the cognitive restructuring module, self-esteem was particularly high after the sessions for patients with higher levels of impaired awareness of apathy. In psychoeducation the patient is confronted with the reality of the degenerative nature of dementia and the status quo, while in cognitive restructuring the individual perception of the patient is evaluated in a Socratic dialogue. The former might be more threatening for patients with reduced awareness and diminish their self-esteem. This interpretation would be in favour of a defensive coping function of unawareness in order to protect self-esteem. The divergence between the modules could also be explained by the different levels of individualising of the therapy forms, which is less pronounced in psychoeducation. In schizophrenia, a more individualised therapy (Bottlender & Hloulal, 2010) and in patients with acquired brain injury settings with feedback using guided experience in a Socratic dialogue (Schrijnemaekers et al., 2014) are preferred to improve



awareness. As Socratic dialogues are characterised by a non-directive, patient driven exploration of thoughts and attitudes, possibly, a changing perspective of the situation is possible acknowledging individual coping strategies of the patient.

After sessions targeted at couples counselling the association with the subscale ‘bond’ differed significantly from the remaining modules. Patients with more impaired awareness perceived especially in couples counselling that the therapist underestimated their problems. We assume that the setting in couples counselling could put patients with impaired awareness under more pressure, because there are two counterparts, the caregiver and the therapist. As impaired awareness is measured by rating discrepancies between caregiver and patient, higher unawareness indicates different perceptions in the couple. Possibly, these differences play a particularly prominent role in the therapeutic process of couple related sessions. Caregivers of patients with impaired awareness are often burdened (Turró-Garriga et al., 2013) and might build an alliance with the therapist to attain patients’ awareness. In exchange, these patients might feel more offended and could perceive less therapeutic bond.

Moreover, we suppose that these components of the patient’s view of the therapeutic process reflect social aspects as mentioned in the biopsychosocial model, which contain dimensions of experience such as stigma or exclusion, and the influence of social and cultural representations (Ownsworth et al., 2006). This may indicate that the therapist should consciously deal with aspects of the relationship and should invest more effort to establish a therapeutic alliance in treating patients with impaired awareness and use preferably a more individual approach.

### **Effect on Awareness**

With respect to the second aim of our study, the data indicated that apathy rating discrepancy remained stable in the CBT condition and decreased in the TAU condition. This

change can be attributed to the increase of the patients' apathy ratings in the TAU condition, whereas the caregiver ratings did not change through the treatment. Under the assumption that a positive rating discrepancy corresponds to impaired awareness, the present study provides preliminary support for increasing awareness of apathy via TAU in AD. On the other side, stabilisation of apathy, in the face of disease progression, may indicate that the treatment is beneficial even without evidence of improvement (Brodaty & Burns, 2012). Patients confronted their apathy symptoms in both conditions (CBT and TAU), but only the patients of the CBT group developed strategies to reduce these symptoms. Hence, it remains unclear whether these effects result from a change in awareness of apathy or a change in apathy symptoms. Previous studies reported that apathy seems to increase in patients with impaired awareness over time (Mograbi & Morris, 2014; Starkstein et al., 2010). Therefore, we assume that the stability of the apathy self-ratings in the CBT condition could be based on both, the reduction or stabilisation of apathy symptoms and an increase of awareness. The stability of the caregiver apathy rating indicates that the caregivers did not notice the achieved behavioural gains of the patients. According to Stella et al. (2015) caregivers of patients with mild AD especially have incomplete perception of the patients' neuropsychiatric symptoms.

It is important to note that results did not show a change in the clinical insight rating, a clinician rating based second measure of the patients' awareness regarding symptoms of AD. The divergent development of the clinical insight rating and the apathy rating discrepancy and their relatively low correlation ( $r = .34$ ) could reflect domain specificity (Leicht et al., 2010) or distinct method variance (Clare, 2004).

Our findings were in favour of the view of rating discrepancies as not only reflecting unawareness but as including a variety of different components such as patient and caregiver characteristics and aspects of the relationship (Nelis et al., 2011; Pfeifer et al., 2013). Thus, particularly when processes over time are taken into account, it is worthwhile to consider both

components of the rating discrepancy separately – the self-rating and the informer rating. Interpreting rating discrepancy should be undertaken in a firm theoretical framework including the different components of rating discrepancy as characteristics of the caregiver and the relationship. Further research is needed to gain more insight into possible indicators for contextual aspects suggesting different interpretations of the rating discrepancies and their function. Interpreting the results of our study as a whole, one might argue that our results suggest that in the context of a therapeutic process convergence of the caregiver and the patient ratings do not necessarily reflect beneficial processes.

There were several limitations to this study. Firstly, the low sample size ( $n = 30$ ) limits the statistical power of the study. The findings should be replicated in the future with a full sample ( $n = 50$ ) or even a larger sample. Secondly, the limitation of a sample comprising voluntary participation in a psychosocial intervention study might lead to selection bias. It is possible that patients with severely impaired awareness or patients without therapy motivation chose not to participate in the intervention study. Further, all patients had caregivers with sufficient resources for participation, which may have also biased the findings. Considering these limitations, it is nevertheless noteworthy that we found medium-to-high effect sizes in a rather small sample. Also remarkable is the relatively low drop-out rate in the CBT group, as almost all patients completed the treatment. Furthermore, to our knowledge, this is the first randomised controlled trial in this context, and therefore our study contributes to providing a better understanding of awareness in relation to a psychosocial multicomponent treatment in early-stage AD.

This study provides evidence of the influence of awareness on the therapeutic process in AD. The effectiveness of a treatment could be raised when considering the level of awareness and adapting the therapeutic work to the special needs of patients with more impaired awareness, for instance by reinforcing therapeutic alliance, clarifying motivational aspects,

using more individualised techniques, and counselling caregivers. Our results highlight that in patients with impaired awareness motivational non-directive treatments may be indicated with the function of reducing denial, as postulated by a psychological component of impaired awareness (Ownsworth et al., 2006). Further research is needed to explore the relationship between awareness and psychosocial interventions in AD in more detail with a particular focus on characteristics of the caregiver and his or her view on the situation. Furthermore, our findings indicate domain specificity, i.e. awareness of apathy seems to be affected by the treatment, especially in the TAU condition, while awareness of AD specific symptoms did not change. Therefore, it is of great importance to evaluate in further studies different kinds of interventions in relation to impaired awareness of different domains, particularly as enhancing awareness would be beneficial for the patient's well-being (Vogel et al., 2010).

In conclusion, the findings of the present study pave the way for future research on awareness in relation to interventions in AD and suggest that it may be of real benefit to consider the level of awareness in treating individuals with AD and their social context.

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## 7 CURRICULUM VITAE

Name: Livia Pfeifer

Date of birth: 25. July 1977

Nationality: Swiss

### Education

- |                   |   |
|-------------------|---|
| 06/2010 - present | University of Zurich, Department of Psychology, Division of Psychopathology and Clinical Intervention<br><i>Doctoral Studies</i><br>Advisors: Professors Dr. Dr. Andreas Maercker, Dr. Simon Forstmeier and Dr. Mike Martin |
| 10/2003 - 11/2009 | University of Zurich, Department of Psychology, Division of Neuropsychology<br><i>Master of Science UZH</i> (equivalent: Licentiata philosophiae)   |
| 08/2001 - 07/2003 | Kantonale Maturitätsschule für Erwachsene, Zurich<br><i>Matura</i>  |
| 08/1993 - 08/1996 | KV Zurich Business School<br><i>Apprenticeship</i>  |

### Professional Activities and Research Experience

- |                   |  |
|-------------------|--|
| 06/2010 - 09/2013 | University of Zurich, Department of Psychology, Division of Psychopathology and Clinical Intervention<br><i>Research assistant</i> |
| 04/2010 - 05/2010 | University of Zurich, Centre for Gerontology<br><i>Scientific Associate</i>  |
| 01/2008 - 07/2009 | Municipality of Illnau-Effretikon, Tax Office<br><i>Registrar</i>  |
| 09/2007 - 02/2008 | Swiss Federal Institute of Technology (ETH), Institute of Behavioral Sciences<br><i>Student research assistant</i>                 |

|                   |   |
|-------------------|---|
| 06/2007 - 07/2007 | Psychiatric University Hospital Zurich, Centre for Addictive Disorders,<br><i>Clinical internship</i> |
| 02/2007 - 05/2007 | University Hospital Zurich, Division of Neuropsychology,<br><i>Clinical internship</i>                |
| 08/1996-10/2006   | Various tax offices in the canton of Zurich<br><i>Registrar</i>                                       |

## **Publications**

### *Peer reviewed articles*

Pfeifer, L., Drobetz, R., Fankhauser, S., Mortby, M. E., Maercker, A. & Forstmeier, S. (2013).

Caregiver rating bias in mild cognitive impairment and mild Alzheimer's disease: impact of caregiver burden and depression on dyadic rating discrepancy across domains. *International Psychogeriatrics*, 25, 1345-1355.

Pfeifer, L., Horn, A.B., Maercker, A. & Forstmeier, S. Caregiver perception of apathy in patients with mild cognitive impairment and Alzheimer's disease: a longitudinal study. Manuscript submitted for publication.

Pfeifer, L., Horn, A.B., Roth, T., Savaskan, E., Maercker, A. & Forstmeier, S. Impaired awareness of apathy in mild Alzheimer's disease: process and effect of a multicomponent cognitive-behavioural treatment. Manuscript submitted for publication.

### *Poster and oral presentations*

Pfeifer, L. (April, 2015). *Urteilerdiskrepanzen zwischen Patienten mit beginnender Alzheimer-Demenz und deren Angehörigen*. Oral presentation at the vierteiliger Zyklus 2015, Forum für Gerontologie, Zürich, Switzerland.

Pfeifer, L., Drobetz, R., Fankhauser, S., Mortby, M.E., Maercker, A., Forstmeier, S. (October, 2012). *Impact of caregiver burden and depression on rating discrepancy across domains in mild cognitive impairment and early-stage Alzheimer's disease*. Oral presentation at the 22nd Alzheimer Europe Conference, Vienna, Austria.

Pfeifer, L., Drobetz, R., Fankhauser, S., Mortby, M.E., Maercker, A., Forstmeier, S. (November, 2011). *Prädiktoren des Belastungserlebens von Angehörigen von Personen mit leichter kognitiver Beeinträchtigung (MCI) oder leichter Alzheimer-Demenz (IAD)*. Poster presentation at the DGPPN Kongress 2011, Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde, Berlin, Germany.

Pfeifer, L. (November, 2010). *Impaired awareness; benefit or barrier for a psychotherapeutic intervention in early-stage AD?* Oral presentation at the 3rd Young Researchers' Meeting 2010, Alzheimer Forum Schweiz, Interlaken, Switzerland.

### **Awards**

Vontobel-Preis für Alter(n)sforschung, 2013

### **Teaching**

University of Zurich, Division of Psychopathology and Clinical Intervention:

|                   |   |
|-------------------|---|
| 02/2013-05/2013 / | Seminar "Klinische Gerontopsychologie: Ausgewählte Störungsbilder |
| 02/2012- 05/2012  | und Interventionen"   |
| 09/2012-12/2012   | Seminar "Fallbezogenes Lernen in der Psychopathologie"            |